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96

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ANNALS

OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

ANNALS CLASSIC. FORTY QUESTIONS IN OTOLARYNGOLOGY. (SUGGESTION BOX FOR YOUNG INVESTIGATORS) (1951)

EFFECT OF BLOOD TRANSFUSION ON RECURRENCE OF HEAD AND NECK CARCINOMA

FASCIA AND PERICHONDRIUM ATROPHY IN TYMPANOPLASTY AND RECURRENT MIDDLE EAR ATELECTASIS

COMPUTER RECOGNITION OF BRAIN STEM AUDITORY EVOKED POTENTIAL WAVE V BY A NEURAL NETWORK

CLEARANCE FUNCTION OF EUSTACHIAN TUBE AND NEGATIVE MIDDLE EAR PRESSURE

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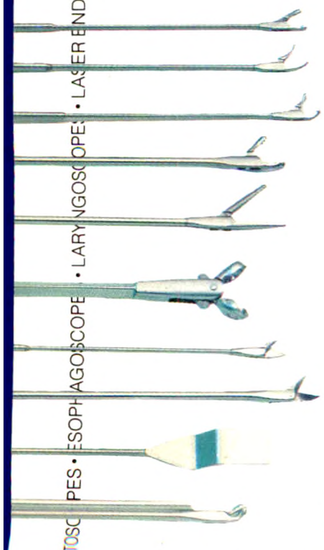

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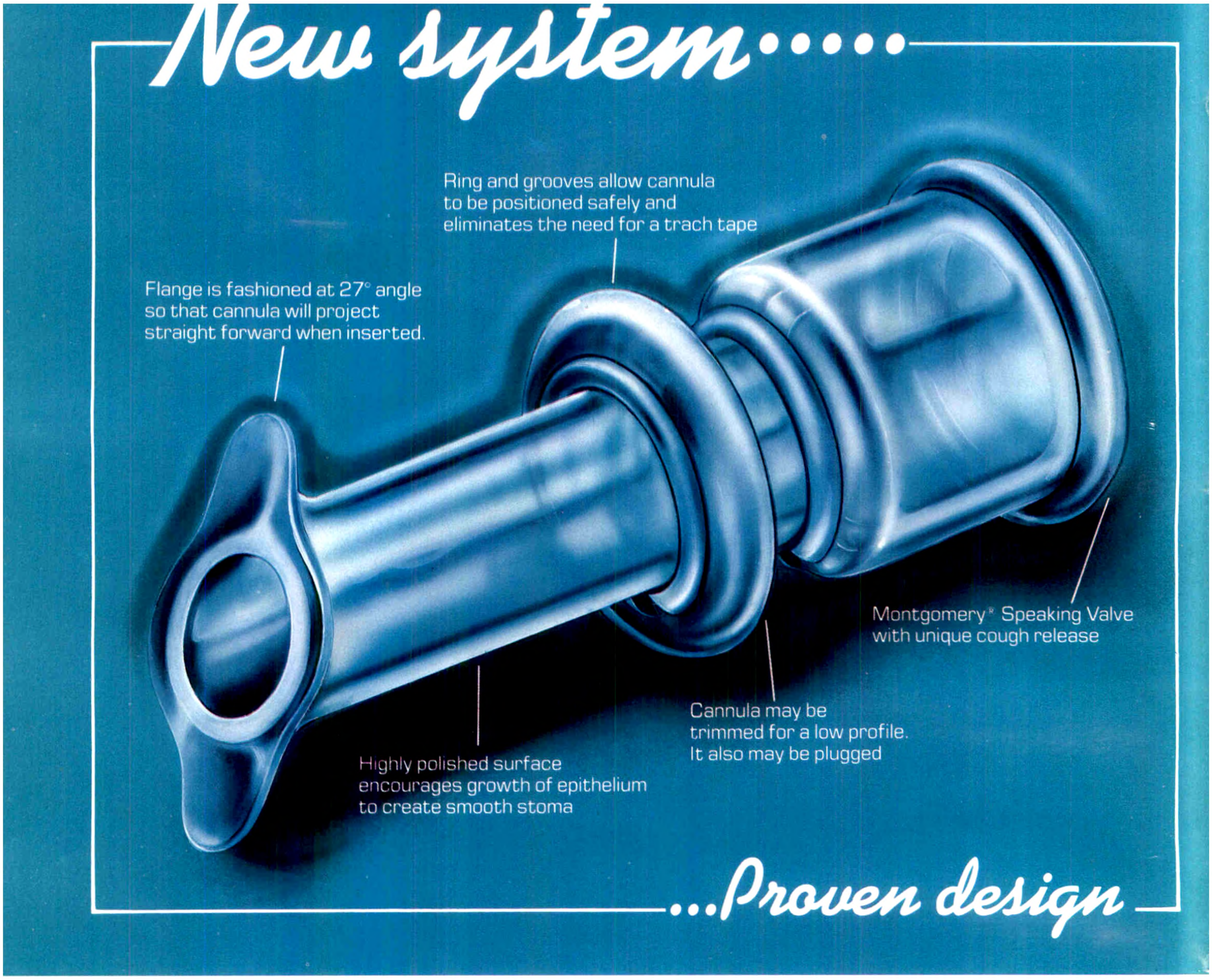

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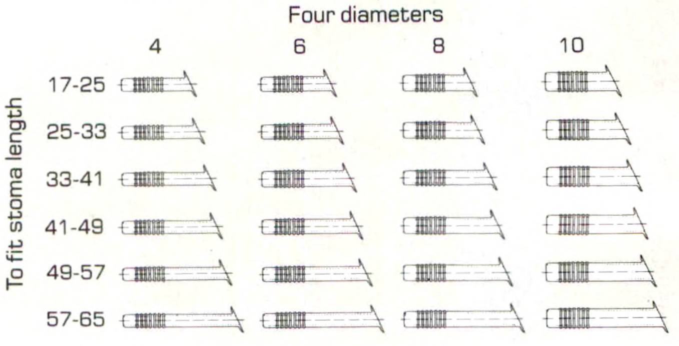

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VOLUME 101 SEPTEMBER 1992 NUMBER 9

CONTENTS

ANNALS CLASSIC

Forty Questions in Otolaryngology. (Suggestion Box for Young Investigators)
Arthur W. Proetz, MD 715

FROM THE AMERICAN LARYNGOLOGICAL ASSOCIATION

Effect of Blood Transfusion on Recurrence of Head and Neck Carcinoma. Retrospective Review and Meta-Analysis
Audie L. Woolley, MD; Norman D. Hogikyan, MD; George A. Gates, MD; Bruce H. Haughey, MB, ChB; Kenneth B. Schechtman, PhD; John L. Goldenberg, MD 724

Phonation and Swallowing Considerations in Pediatric Laryngotracheal Reconstruction
Marshall E. Smith, MD; Anthony J. Mortelliti, MD; Robin T. Cotton, MD; Charles M. Myer III, MD 731

FROM THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

Consumer Product Aspiration and Ingestion in Children: Analysis of Emergency Room Reports to the National Electronic Injury Surveillance System
James S. Reilly, MD; Margaret A. Walter, MD 739

Pediatric Airway Manifestations of Gastroesophageal Reflux
Deborah Mitchell Burton, MD; Seth M. Pransky, MD; Richard M. Katz, MD; Donald B. Kearns, MD; Allan B. Seid, MD 742

INDEPENDENT CONTRIBUTIONS

Distributions of Eustachian Tube Goblet Cells and Glands in Children With and Without Otitis Media
Shoji Matsune, MD, DMSc; Isamu Sando, MD, DMSc; Haruo Takahashi, MD 750

Fascia and Perichondrium Atrophy in Tympanoplasty and Recurrent Middle Ear Atelectasis
Richard A. Buckingham, MD 755

Clearance Function of Eustachian Tube and Negative Middle Ear Pressure
Haruo Takahashi, MD; Iwao Honjo, MD; Masahiko Hayashi, MD; Akihiko Fujita, MD 759

Chondroblastoma of the Temporal Bone. Case Report and Literature Review
Mark A. Varvares, MD; Mack L. Cheney, MD; Max L. Goodman, MD; Emily Ceisler, MD; William W. Montgomery, MD 763

Organ-Limited Laryngeal Amyloid Deposits: Clinical, Morphological, and Immunohistochemical Results of Five Cases
Godber Sönke Godbersen, MD; J. Friedemann Leh, MD; Martin L. Hansmann, MD; Heinrich Rudert, MD; Reinhold P. Linke, MD 770

New Device for Interdental Immobilization
Boris O. Divis, MD, FRCSC 776

Carotid Artery Resection for Head and Neck Cancer
Michael D. Maves, MD; Matthew D. Bruns, MD; Michael J. Keenan, MD 778

COMPUTER APPLICATIONS IN OTOLARYNGOLOGY

Computer Recognition of Brain Stem Auditory Evoked Potential Wave V by a Neural Network
Donald T. Freeman, MS 782

IMAGING CASE STUDY OF THE MONTH

Intraparotid Hematoma
Arthur M. Lauretano, MD; Michael J. Cunningham, MD; Alfred L. Weber, MD 791

PATHOLOGY CONSULTATION

Amyloidosis in the Upper Aerodigestive Tracts
A. Kevin Raymond, MD; Nour Sneige, MD; John G. Batsakis, MD 794

OBITUARY

Bruce Proctor, 1914-1992 797

MISCELLANEOUS

Letters to the Editor 798

Information for Subscribers 2a

Instructions to Authors 17a

Index to Advertisers 20a

This article originally appeared in September 1951, Volume 60, No. 3, pages 648-656, and is reproduced here in its entirety.

FORTY QUESTIONS IN OTOLARYNGOLOGY

(SUGGESTION BOX FOR YOUNG INVESTIGATORS)

ARTHUR W. PROETZ, M.D.

ST. LOUIS, MO.

A fool can pose questions wise men cannot answer.

Fortunately for me, I have been cast today in the former role, and it should be no arduous task to propound some thirty or forty questions for your solution.

To be sure, answers have been forthcoming to most if not all of my questions, for the medical man through the ages must have an answer to everything, no matter how implausible. Furthermore, I am convinced that some of our most widely accepted "truths" will be modified in the future, as they have in the past. Observes Wright, "Some of the passages in the writings of the Aesclepiadae seem ridiculous to us, but we should keep constantly in mind the charity which our successors in their histories will have to extend to the productions of our own times. Indeed, in looking over the various commentaries on Hippocrates from Galen's time to our own, it is curious and not a little amusing to observe how careful each critic is to point out the errors Hippocrates committed in not being in accord with the doctrines of the critic's own time, which are now as obsolete as those of Hippocrates."

To just what degree the following problems may have approached solution is apt to be a matter of personal opinion, depending upon whether one finds acceptable or not the best investigations to date. Let us begin with the nose:

No. 1. What is the nature of the sense of smell? Publications on this subject, which between 1850 and 1900 reached to almost 900, have dwindled to a mere handful since the turn of the century now half-gone. One reads of sporadic experiments with insects, but they do not improve materially upon those of Fabre, and it is still an open question whether the olfactory function is chemical in

---

Read before a joint meeting of the Section on Otolaryngology of the Southern Medical Association and the St. Louis Nose and Throat Club, November 16,, 1950.

nature, or the result of vibrational resonance, or neither, or possibly a little of both.

No. 2. The function of the sinuses. Textbooks still mention these casually as "adding resonance to the voice," "heating inspired air," "moistening inspired air," "redistributing air" (whatever that may mean), and "lightening the skull." Two of these apply in an unimportant degree, the rest can be demonstrated as false. That sinuses serve in keeping the heads of terrestrial animals afloat when they are forced to take to the water, that they act as insulators against heat and cold, and that they occur incidentally during the repositioning of facial bones after ossification has taken place: all of these are true, but may be incidental to some more fundamental purpose.

No. 3. Origin of sinuses. Are they the result of a primordial urge of the nasal mucosa to invade bone as has been suggested? Probably not. Absence of osteoclasts makes it unlikely that they result from a hollowing-out of bone such as has been described in the so-called bony cysts of the turbinates. To say that they are the result of the natural processes of growth explains nothing. It was "known" until very recently that their early development can be stunted by infection, as noted by Wittmaack in the case of the mastoid cells. Now this is seriously questioned.

No. 4. The nature of ostia—why are they present and why so small?

Obviously it is necessary to have some communication between the rigid sinus cavities and the atmospheric air in order to prevent pressure disturbances, and presumably the smallest possible opening is desirable to render the cavity as nearly closed as possible, and still to permit interchange of air. This latter assumption gains weight from the fact that in the dog's frontal sinus, for example, there is a thin lamina, a partial septum, rendering the inlet more tortuous, and reducing the free circulation of air.

It is unexplained also why the cilia change their direction of beat in the region of the sphenoidal ostium during the formation of the sinus, so that in the upper portion of the cavity ciliary beat will not be away from the ostium, as it would have been without this change of direction.

No. 5. Vacuum in the sinuses. There are several theories for this. First the absorption of air, which is difficult to prove unless a *specific* absorption takes place, which has not been demonstrated. The normal interchange of gases should result in a slightly positive, instead of negative, change in pressure. It is possible that the swelling of the mucosa may drive out the air, and that the region of the ostium may remain swollen and closed, while there is a recession of the edema elsewhere. This is logical but so far unproven. Hilding has shown further that the ciliary propulsion of thick mucus, out through an ostium, may occur faster than it can be replenished by the glands and thus produce negative pressure.

No. 6. What is a sinus headache? Presumably the result of tension produced by a vacuum, but experiments suggest that the sinus lining is not sensitive except in the neighborhood of the ostium. Whether this applies to an inflamed mucosa, as well as a normal one, has not been made quite clear. There is evidence that a positive pressure may exist in an obstructed sinus during headache.

No. 7. There is much that remains unknown regarding nasal cilia. Why do they beat, always, in one direction? What makes them beat at all? It has been shown that in some of the lower animals continuity of wave propagation is a nerve function. In the human, however, no continuous waves occur and since cilia may persist in beating upon a single cell, or even a cell *fragment* after that cell has been teased away from the the general mass in a culture medium, the beat impulse must be inherent in the cell. It remains unexplained also why the ciliary beat is always toward the pharynx and why, after an injury or denudation, the direction of beat in the new tissue conforms to that in the old. Also, why does normal regeneration sometimes occur after a complete stripping of the sinus wall and at other times fail completely?

No. 8. Congenital choanal atresia. Why is it that in this condition although obstruction persists for many years, infection and hyperplasia of the nasal structures and the eustachian tube do not take place, although these are characteristic of obstruction brought about by other agencies which have their beginnings some time after birth?

No. 9. What is the nature of a sneeze? Is it the cause or the effect of sudden changes in the engorgment of the turbinates? The accompanying "goose flesh," which pervades other portions of the body the same time, would indicate the latter; or would it?

No. 10. What is the nature of the superposition of stimuli by which a half-baked sneeze can be brought to fruition? This seems to be effective only if the added stimulus is one of light. A similar reaction does not follow strong taste stimuli such as salt on the tongue, or tactile ones such as a finger prick; in fact, sharp noise may serve to sidetrack the half-developed sneeze.

I know of a case, however, in which moderate tactile stimulation with the finger or with a hair brush at the hairline in the frontal region will promptly and invariably produce sneezing.

No. 11. Cerebrospinal rhinorrhea. What are the causes and the nature of the spontaneous type? Why is it likely to be intermittent? What prevents prompt infection of the meninges?

No. 12. What are the effects of the endocrines on the respiraatory system? There is evidence that the pituitary and the adrenal glands influence the status of the nasal mucosa in some degree and under some circumstances. It has been shown that the thyroid hormone, and especially the lack of it, produces altered tone and an increased sensitivity to infection and histamine. The exact mechanism of these phenomena has not been explained.

No. 13. The intimate connection between the nose and the genital organs has received not infrequent attention, but the nature of these relations remains vague. So-called vicarious menstruation from the nose has latterly been interpreted as merely nonspecific bleeding, resulting from the general congestion. Vascular changes in the nose accompanying genital tumescence and detumescence may fall into the same category. The recurrence of polyps during successive pregnancies also requires explanation. In the late '90s Fliess wrote a monograph on the relationship of the nose and the genital tract; however, he allowed himself to be caried away by his subject to a point which made it difficult to distinguish between fact and fancy, thus greatly impairing the value of his work.

No. 14. Atrophic rhinitis. Practically everything about this disagreeable disease requires explaining; its cause, the nature of the atrophy and above all the treatment. This last falls into two methods of approach, the mechanical reduction of the air spaces and the attempted regeneration of the mucosa through the administration of the female hormone. The first is only partly successful; the second, based on purely theoretical grounds, even less so.

No. 15. Idiosyncracies to drugs. In rhinological practices the hypersensitivity to cocaine and pontocaine is probably the most serious. Idiosyncracies to atropine, codeine, aspirin and morphine can be troublesome. In this connection may be mentioned also that terrifying but quite hypothetical condition formerly designated as "status lymphaticus."

No. 16. The relationship of sinusitis to retrobulbar neuritis. Considerable controversy has arisen from time to time as to whether or not such relationship exists. It has been both affirmed and denied by observers of more than average ability. A direct connection between the nasal sinuses and the optic nerve has been described. Usually the effect of nasal operations upon the condition have been attributed to the resulting decompression. Leon White, who devoted much of his life and work to the study of the relationship between the optic nerve and its foramen, and was convinced that the pressure of a small foramen could be responsible for the condition, was later obliged to concede (and had the courage to do so) that he was mistaken.

No. 17. Sinuses and mental disease. Some fifteen years ago two English investigators, Pickworth and Graves, through a series of published papers stimulated considerable interest in the possible relationship between infected sinuses and the various delusional states. Apparently little was done by others, either to confirm or to disprove their contentions, and the problem, still unsolved, seems to have disappeared from the medical prints.

No. 18. The sinuses and rheumatism. The position of the sinuses in the rôle of foci of infection has not been well established, although most writers regard it as relatively unimportant. Writers are agreed that where sinus infection exists, in cases of rheumatism and other similar remote affections, it should surely be eradicated. They are less in agreement regarding the results obtained.

No. 19. Juvenile nasofibroma. This fearsome tumor requires explanation both as to etiology and location. Springing as it does from a region not especially vascular, its structure also requires explaining. The details of its management are likewise controversial especially regarding the value of irradiation either with or without subsequent surgery, the method of removal, and the necessity of preliminary carotid artery ligation.

No. 20. Malignant granuloma. This uniformly fatal lesion defies classification and treatment. The most recent comprehensive review of the condition is probably that which Lierle published some three years ago. The prognosis is still hopeless.

No. 21. Familial telangiectasis. This is another of the distressing and sometimes fatal conditions of undetermined cause and development. This hereditary deficiency in the components of the vascular walls is probably best managed at the present writing by the persistent, painstaking and systematic application of high-frequency desiccation as described by Figi, although the treatment cannot be said to be universally accepted.

No. 22. The common cold. Despite the antihistamine bubble which has burst damply in our faces, the common cold continues an unsolved problem. We do not know what it is, how to prevent it, or how to cure it.

No. 23. The function of the tonsil. A generation or so ago, the question of tonsil function was uppermost in many minds. It was suggested that the tonsil is a hemopoietic organ; that it is a filter against bacteria; that it has an internal secretion; that it elaborates antibodies from absorbed bacteria. Wright discovered, for example, that bacteria which did not ordinarily penetrate the tonsil could be made to do so by coating them with butter, an interesting observation which aroused only passing attention.

No. 24. The action of the epiglottis. In earlier days it was assumed without much actual investigation that the epiglottis was a trap door to prevent the entrance of food and other solid material down the glottic chink. Later it was authoritatively stated that the epiglottis was actually a rigid structure which protected the glottis by diverting food and drink to the sides and into the pyriform fossae, and it was pointed out that no muscles exist which could turn down the epiglottis as a trap door.

Only last spring, in San Francisco, a strip of radiological motion pictures was exhibited by Saunders and his associates which seemed to show that the larynx rising during deglutition forced the epiglottis against the tongue in such a manner as to tilt it backward to cover the glottis. Some of the foremost endoscopists are still not convinced by the demonstration, and the action of the epiglottis remains among the unsolved problems.

No. 25. The purpose of a yawn. The nature of this interesting phenomenon is not only unexplained in most texts on physiology, but is completely ignored. It is not to be found in the indexes of any of the volumes at my disposal. The dictionary shrugs it off as "an involuntary deep inspiration with the mouth open:" a feeble definition, if I ever saw one.

It would appear at first consideration that this deep inspiratory effort might be for the purpose of increasing the oxygen intake, but since it lasts three or four times as long as a normal inspiration it would seem to defeat its own purpose.

No. 26. The eustachian orifice and its environs. This problem, which seemed completely solved for many years until the exigencies of aerial warfare once more focused attention upon it, seems still to require some investigation. The causes of so-called aero-otitis media and the attempt to combat it by irradiation of its lymphoid constituents evoked a more careful study of the distribution of these tissues. Some, as yet unpublished, work by Semenov delves further into the unknowns of this region.

No. 27. Lingual pain and the menopause. The onset of unexplained glossopharyngeal neuralgia at and after the menopause requires explanation as does the self-limiting nature of this excruciating pain.

No. 28. Parageusia in the aging. Probably closely associated with the last category of symptoms is the bitter taste complained of by women in the fifth and sixth decades of life. The presence and the self-limitation of the symptom require explanation, as does the fact that it occurs almost exclusively in women.

No. 29. The nature of the passage of infection between the pharynx and the trachea. It has always been taken more or less for granted that infectious material from the upper respiratory tract passed through the lower, directly, via the chink of the glottis. However, large masses of such material must undoubtedly set up a bechic reflex to expel them, and microscopic quantities deposited in the upper trachea would inevitably be raised to the glottis by the action of the cilia in that region. Furthermore, we are taught that no lymphatics traverse the vocal cords. A discussion of the question invariably brings the answer "well it occurs during sleep," but if the bechic reflex is lulled to rest at such times the breathing is also quiet and the cilia are still active.

It might be pointed out that while a sudden explosive *expiratory* blast occurs, which we call a cough, there is no comparable inspiratory blast to carry infectious material *into* the trachea. It seems quite likely that infection from the bronchial tree to the nose occurs quite as frequently as the opposite.

The lymphatic connection between the upper respiratory tract and the deeper pulmonary glands has been shown; not so, any connection with the upper trachea.

No. 30. The management of bilateral recurrent paralysis. The multiplicity of methods suggested for the remedy of this condition still leaves it in the category of unsolved problems. The details are many and intricate and so are the articles dealing with them.

No. 31. Papilloma laryngis. Since the cause of this condition is unknown, the management is still empirical and not too satisfactory. Repeated removal is still required. The endocrine approach, based upon theoretical concepts, is not meeting with the anticipated success.

No. 32. Cancer of the larynx, its origin, its spread, and its treatment. Conferences upon this subject have much the flavor of conferences held ten (and twenty) years ago: irradiation, what kind, and how much? Surgery, what kind, when, and how extensive.

No. 33. Tobacco and pulmonary cancer. The connection is thus far inferential. That there has been a sudden increase in bronchial and pulmonary cancer in the last three decades is a fact. That cigarette smoking has increased enormously in the same time is a fact. That the increase in bronchial cancer occurs in nonsmokers as well as smokers is a fact. That the relationship between the two has not been established is regrettably also a fact.

No. 34. The nature of hearing. The earlier theories of hearing were based largely upon models of the cochlear apparatus, and on hearing tests. The discovery of the Wever-Bray phenomenon permitted and stimulated a new type of research. Many investigators, among whom the names of Lorente de No, Davis, and Hallpike spring to mind, are busy with the problem.

No. 35. Absolute pitch. Why some persons have the ability to recognize the pitch of a tone as most of us recognize a color remains unexplained. Colorblindness is the exception. Pitchdeafness the rule.

No. 36. Diplacusis. When we solve the problem of sound perception then the nature of diplacusis will be better understood. It is possible that the observation of conditions in diplacusis may help to establish and confirm theories of hearing.

No. 37. Musical interpretation centers. The complex mechanism of musical perception and conception is still a closed book. I know of at least one case in which a cerebral accident deprived an individual of his ability to read notes while he continued to recognize melodies by ear and also retained his sense of absolute pitch.

No. 38. The cause of tinnitus. Once we learn to recognize and to differentiate the causes of this distressing symptom we may be able to prevent it and to abandon our present desperate remedy, the euthanasia of the eighth nerve.

No. 39. The interpretation of high-tone loss and other similar acoustical phenomena. The acoustics of the skull are complicated and variable. It is understandable that a similar high-tone loss may occur in such disparate conditions as nerve degeneration and fluid in the middle ear on this ground. Demonstration of the process is still wanting.

No. 40. Otitis externa diffusa, the nature of cerumen, and aberrations of the skin of the canal and its glands are among the problems brought into prominence by the war in the Pacific. The work of Senturia promises an early, and we hope effective, solution.

No. 41. The nature of otosclerosis. Concerning this disease we are not without theories—emphatically expressed—some logical and some fantastic, but we are still in the dark as to what it is, how to prevent it, or how to stop its progress. The importance of the problem is indicated by the fact that an organized group exists for its study.

No. 42. The final, burning, sixty-four thousand dollar question: how to keep that new oval window open. Not long ago a group of otologists in South America were discussing the work of an investigator.

"I have spoken with him," said one of the colleagues, "he has the final answer."

Eyebrows went up.

"Do you believe that?" they asked.

"Well," he replied, "he ought to know a final answer when he sees it. This is his *fifth* final answer."

* * *

The fool has asked his questions; let the wise men take over.

Beaumont Medical Building.

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EFFECT OF BLOOD TRANSFUSION ON RECURRENCE OF HEAD AND NECK CARCINOMA

RETROSPECTIVE REVIEW AND META-ANALYSIS

AUDIE L. WOOLLEY, MD NORMAN D. HOGIKYAN, MD GEORGE A. GATES, MD
BRUCE H. HAUGHEY, MB, CHB KENNETH B. SCHECHTMAN, PHD JOHN L. GOLDENBERG, MD
ST LOUIS, MISSOURI

To study the effect of transfusion on recurrence of squamous cell carcinoma of the head and neck, we analyzed the records of 143 patients with stage II through IV squamous cell carcinoma of the supraglottic larynx or hypopharynx for whom follow-up to recurrence or 5 years after surgical therapy was available. Variables studied were age, gender, TNM staging, duration of operation, estimated blood loss, units of blood products transfused, surgical margins, number of pathologic nodes, radiotherapy, chemotherapy, hematocrit, and serum albumin. Multivariate logistic regression demonstrated that transfusion, number of pathologic nodes, and preoperative hematocrit were significantly related to recurrence. The univariate odds ratio for tumor recurrence in patients receiving any blood products was 3.2 (95% confidence interval 1.5 to 6.9; $p = .004$). Based on a meta-analysis of the data from this study and the five published studies, the combined odds ratio for recurrence after transfusion was 2.6 (95% confidence interval 1.9 to 3.7; $p < .0001$). These data identify a clinically important adverse effect of transfusion of blood products on tumor recurrence in patients with advanced head and neck cancer. We recommend a policy of blood conservation surgery to enhance cancer control, and we encourage further research to clarify the mechanism(s) of this effect.

KEY WORDS — blood transfusion, head and neck carcinoma.

INTRODUCTION

The scope of modern surgery has been expanded by a large number of technical developments, among them the use of heterologous blood products. Modern blood tank techniques have reduced the risk of transfusion reaction and of transmission of hepatitis and human immunodeficiency viruses. However, in patients with systemic neoplastic disease, ie, regional metastasis or distant micrometastasis, concern has arisen regarding the possible effect of transfusion on the immune system.

The immunosuppressive effects of blood transfusions were noted as early as 1973, when renal allograft survival was found to be substantially improved in patients who had received prior blood transfusions.[1] This effect was thought to be secondary to immunosuppression induced by exposure to antigens expressed by the transfused white blood cells, either by production of suppressor cells or by graft-versus-host response. The effects of immunosuppression on malignancy are also well known: immunodeficient and immunosuppressed patients show a greater incidence of malignancy.[2-6]

In 1982 Francis and Shenton[5] noted that allogeneic blood transfusion enhanced tumor growth in rats. Burrows and Tartter[6] reported an increased rate of recurrent colon cancer in patients who had received blood transfusions. Since then, several reports[7-14] have demonstrated a relationship between perioperative blood transfusion and recurrence of solid tumors. However, this effect has not been consistent for all tumor types or sites.[15,16] In the head and neck, three retrospective studies have reported an adverse effect,[17-19] and two[20,21] have shown no effect of blood transfusions on cancer recurrence. The variability of study design and material among these reports prompted us to review our own cases and conduct a meta-analysis of the reported data.

MATERIALS AND METHODS

The records of all patients treated surgically for carcinoma of the supraglottis or hypopharynx at Barnes Hospital, St Louis, Mo, from 1975 to 1984 were requested, and the 224 records obtained were reviewed. Excluded were patients with stage I tumors, second primaries, distant metastases, or less than 5 years of disease-free follow-up. The remaining 143 cases of stage II through IV carcinoma of the supraglottis ($N = 85$) or hypopharynx ($N = 58$) constitute the study group. The list of patients was generated from the Head and Neck Tumor Registry of the Department of Otolaryngology. The original records were reviewed to ensure uniformity of staging accord-

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From the Department of Otolaryngology, Washington University School of Medicine, St Louis, Missouri.

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REPRINTS — George A. Gates, MD, 517 S Euclid, Box 8115, St Louis, MO 63110.

TABLE 1. MEAN VALUES AND RANGES FOR 12 VARIABLES ACROSS RECURRENT AND NONRECURRENT GROUPS

	No Recurrence (N = 77)			*Recurrence (N = 66)*			
Variable	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	*p**
Age in years	59.3	9.1	39-75	59.8	9.5	35-81	.743
Proportion of men	0.74			0.82			265
T stage	2.71	76	1-4	2.78	0.85	1-4	.583
N stage	0.52	0.79	0-3	0.92	0.97	0-3	.009
Stage group	3.17	0.79	2-4	3.05	0.72	2-4	.367
Preop hematocrit (%)	43.0	3.8	32-51	41.0	3.6	32-48	.003
No. of positive nodes in surgical specimen	0.69	1.2	0-6	1.7	2.4	0-9	.005
Proportion of patients with histologically positive surgical margins	0.21			0.28			.270
Length of operation (h)	5.3	1.7	2.8-11.7	5.9	1.6	2.8-10.0	.064
Estimated blood loss at operation (mL)	744	493	175-2,500	960	554	150-3,200	.020
Units of blood products	1.3	1.6	0-7	2.5	1.9	0-9	.0001
Proportion of patients with preop or postop irradiation	0.91			0.94			.498

*p value of *t* statistic as determined by univariate logistic regression.

ing to the 1988 American Joint Committee on Cancer.[22] The study was limited to tumors from two adjacent sites to minimize site-related variations in tumor behavior or therapy. Exclusion of patients with stage I cancer was justified by the different treatment policies for these cases, which have a much better prognosis than more advanced disease.

The following variables were recorded. Patient variables were age, gender, serum albumin, and preoperative hematocrit. The TNM parameters used were T, N, and tumor stage; these were based on staging endoscopic descriptions. Estimated blood loss and duration of surgery were the operative data. Operative procedures were supraglottic laryngectomy, total laryngectomy, or partial laryngopharyngectomy; neck dissection was done in two thirds of the cases. Radiotherapy, either preoperative or postoperative, and chemotherapy were noted. Transfusion data included units of packed red blood cells and units of whole blood administered within 2 weeks of the surgical procedure. Because many patients received both whole blood and packed red blood cells, blood products were combined into a single variable. Histologic variables were number of positive nodes and margin status. Serum albumin was normal in all cases but one and was not considered further. Chemotherapy was also excluded from analysis because only three patients were treated, one preoperatively and two postoperatively. Surgical procedures were not analyzed separately.

Univariate analyses were performed with each of the 12 remaining parameters used as an independent variable, with recurrence within 5 years as the dependent variable. The χ^2 test was used for categoric terms, and logistic regression was employed for continuous variables. Those variables from the significant univariate analyses were subsequently entered into stepwise multivariate logistic regression analyses. This allowed for identification of covariation, as well as the influence of each variable on the association of the other variables with recurrence rate. Cox regressions were also done, but are not reported because the results were virtually identical to the logistic analyses and because recurrence within 5 years, not time to recurrence, was the principal factor of interest in this report. Analyses using survival, rather than tumor recurrence, were also conducted but not reported because, in general, the results paralleled the recurrence end points, and because successful secondary therapy might obscure the earlier treatment failure.

Meta-analysis involved two separate sets of calculations. For each study in the meta-analysis the individual odds ratio, 95% confidence intervals (CIs), and significance tests were obtained from logistic regressions of the data from the 2 x 2 tables of number of patients with recurrences and number of patients receiving blood products. In the second step an overall odds ratio was determined by using the present study combined with the five published studies.[17-21] This was based on the standard Mantel-Haenszel[23] approach to combining 2 x 2 contingency tables, each of which is generated from a different study. Assume that a given study enrolls N patients, n of whom receive a transfusion, and r of whom have a recurrence of their disease. For each study, the Mantel-Haenszel procedure compares O, the observed number of recurrences among transfused patients, with $E = nr/N$, the expected number of recurrences among transfused patients. Assuming that the null hypothesis of no effect of the transfusion is correct, the difference $O - E$ will differ randomly from zero and will have variance given by $\mathrm{Var} = E(1 - n/NO)(N - r)/(N - 1)$. If Sumdiff is the sum of the differences $O - E$ over all studies, and if Sumvar is the sum of the variances of these differences over all studies, it

TABLE 2. MEAN VALUES, ODDS RATIOS, 95% CONFIDENCE INTERVAL, AND SIGNIFICANCE LEVELS OF SIGNIFICANT VARIABLES IDENTIFIED BY STEPWISE LOGISTIC REGRESSION AS PREDICTING TUMOR RECURRENCE

Variable	*Mean*	*Beta Coefficient*	*SD*	*p*	*OR (95% CI)*
Units of blood	1.9	0.311	0.118	.009	1.36 (1.08-1.72)
No. of nodes	1.1	0.265	0.111	.009	1.30 (1.04-1.62)
Preop hematocrit	42.0	−0.133	0.053	.014	0.88 (0.79-0.97)

OR — odds ratios, CI — confidence interval.

follows that an estimate of the combined odds ratio is given by Odds Ratio = exp[(Sumdiff − 0.5)/Sumvar]. Also, SE, the standard error of the summed differences, is the square root of Sumvar, so that 95% confidence bounds on the combined odds ratio are given by exp[(Sumdiff − 0.5)/Sumvar ± 1.96/SE].

To estimate bias from unpublished studies we determined the number of studies of similar sample size with an odds ratio of 1 that would be necessary to reduce the overall odds ratio of this meta-analysis to the level at which the 95% CI was less than 1. All published studies of the effect of transfusion on head and neck cancer were included. To our knowledge there are no unpublished studies.

RESULTS

The average age was 60 years, with a range of 35 to 81. One hundred eleven patients (77%) were male. There were 34 stage II tumors (24%), 60 stage III (42%), and 49 stage IV (34%). Overall, 99 patients (69%) received blood products; 66 patients (46%) had local or regional recurrence or distant metastases. The recurrence rate was 41% for the supraglottic cases and 53% for the hypopharyngeal cases; this difference was not significant ($\chi^2 = 2.09$, p = .148). The recurrence rate was 54% in the 99 transfused cases versus 27% of 44 nontransfused cases. The odds ratio for recurrence in the transfused cases was 3.2 (95% CI 1.5 to 6.9; p = .004).

The mean scores and ranges of the 12 independent variables by transfusion status are displayed in Table 1. Five variables were statistically significant single predictors of recurrence: preoperative hematocrit, number of units of blood products, number of metastatic nodes proven by histologic examination, blood loss, and clinical node (N) status.

These five variables were entered into a stepwise multivariate logistic regression. Estimated blood loss and N status were no longer significant and were removed from the model. Blood loss appeared to covary with units transfused, and N status covaried with the number of metastatic nodes. The final multivariate model identified number of units transfused, number of positive nodes, and preoperative hematocrit as significant predictors of recurrence. Table 2 indicates the magnitude and significance of those associations.

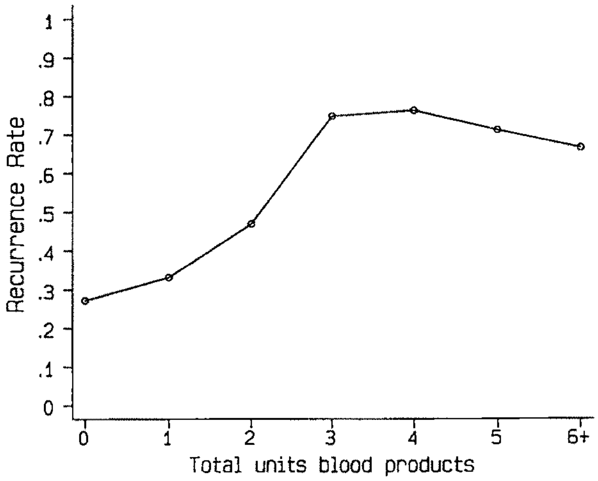

Fig 1. Actual recurrence rate is displayed for each level of transfusion. Total units of blood products includes whole blood and packed cell transfusions. Two patients who received more than 6 units of blood products are grouped with the three who received 6 units. Number of patients for each level of transfusion is 0 units, 44 patients; 1, 24; 2, 34; 3, 12; 4, 17; 5, 7; and 6+, 5. Note substantial difference between those receiving 0 to 2 units and those receiving 3 units or more.

The dose relation between units transfused and crude recurrence rate is displayed in Fig 1. Recurrence rate increases markedly between 2 and 3 units, and remains fairly steady beyond that level. There was also a greater rate of recurrence with increasing numbers of metastatic nodes, with a notable increase in rate between two and three positive nodes (Fig 2).

The results of the meta-analysis of the effect of blood transfusion on tumor recurrence are displayed in Table 3[17-21,23] and Fig 3.[17-21] The overall odds ratio for recurrence was 2.65 (95% CI 1.88 to 3.72; p < .0001). Twenty-five negative studies of comparable size and design with an odds ratio of 1 were found to be necessary to reduce the combined odds ratio to the level at which the lower bound of the 95% CI was less than 1.

DISCUSSION

The design of the current study permitted multivariate analysis of the major known determinants of cancer recurrence. Squamous carcinoma of the supraglottic larynx and hypopharynx is associated with moderate differences in survival between the two sites, even though patterns of recurrence are similar. The two sites are related anatomically, and a

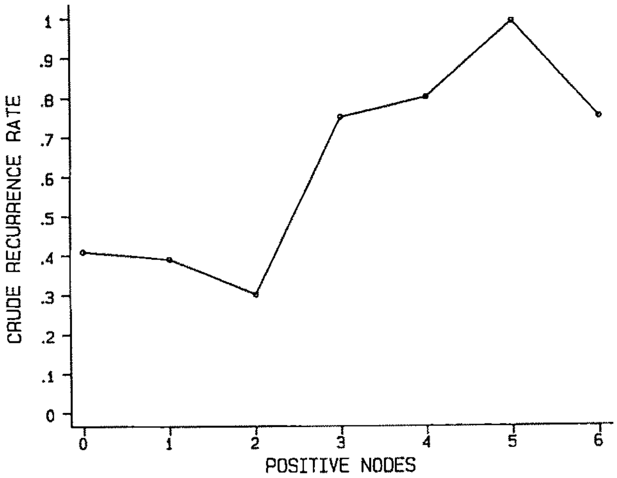

Fig 2. Actual recurrence rate is displayed for each level of number of metastatic nodes identified in surgical specimen. Eighty-one patients were N0 histologically or did not have neck dissection; 28 had one node; 10 had two; 8 had three; 5 had four; 3 had five; and 8 had six or more nodes. Note marked difference between those patients with no nodes or one or two nodes and those with three or more.

tumor at one site frequently involves the other and vice versa. Indeed, many tumors involved both sites. These similarities helped reduce treatment variations to a minimum. All operations were done by otolaryngologists trained under the same philosophy and using the same technical approach.

Cancer control is a complex process that depends on three groups of clinical factors: patient, tumor, and treatment. In this study, an important variable from each group was identified as a factor for tumor recurrence. The chief patient factor was abnormal preoperative hematocrit. The most important tumor factor was the number of metastatic nodes, with three or more nodes as a critical level. The most important treatment factor was units of blood transfused, with 3 units or more as a critical level. These relations were maintained after adjustment for the levels of each of the other two variables. Because inferences about causation based on statistical analysis must always be made cautiously within the framework of knowledge about the pathophysiology of malignant disease, the following interpretations of the observations from this retrospective review are offered.

A low preoperative hematocrit is a general sign of ill health and may reflect the poor nutritional status that is so common among patients with head and neck cancer. Nutritional status is known to affect immune competence as well.[24]

The effect of metastatic nodes on treatment failure is well documented.[25-27] Nodal disease places a burden on the immune system, and the finding that nodal disease affects recurrence is entirely consistent with current theory. Contrary to theory, however, was the lack of effect of tumor (T) stage on recurrence in the present case, even with the observed increase in N stage and number of nodes with increasing T stage. Given the types of aggressive surgical therapy and radiotherapy used in these patients, it might be the case that the effects of tumor size were overcome by escalated therapy. An alternative interpretation is errors in staging. However, we reviewed the original records and restaged all cases using the 1988 AJC classification to ensure against this possibility.

The pathophysiologic effect of blood transfusion on cancer recurrence after treatment is still incompletely understood. One obvious interpretation is that transfusion is a covariate of tumor extent: larger tumors are associated with large operations, long operative time, and greater blood loss. Larger tumors have a potentially greater effect on host immunity, in addition to the immunodepressive effects of anesthesia[28] and surgery.[29] Therefore, one could argue that the transfusion effect is simply a reflection of tumor size. Indeed, there was greater blood loss and increased transfusion use with increasing stage of tumor. However, the multivariate analysis, which permits an examination of each factor while controlling the effects of the other factors, indicated that neither tumor stage nor duration of operation had a significant effect on recurrence in this patient population, whereas units of blood transfused did.

Therefore, these data provide support for the theory that transfusion has a direct effect on recurrence. A plausible mechanism for this effect is immunosup-

TABLE 3. META-ANALYSIS OF EFFECT OF TRANSFUSION ON TUMOR RECURRENCE

Study	*No. Pts*	*Recur*	*Trans*	*Var*	*O–E*	*OR*	*95% CI*
Johnson et al[17]	139	0.39	0.84	4.43	2.55	1.86	0.68- 5.08
Jackson and Rice[18]	100	0.39	0.41	5.81	12.00	9.40	3.70-23.80
Jones and Weissler[19]	94	0.43	0.51	6.15	7.94	6.18	2.86-15.50
Böck et al[20]	161	0.16	0.83	3.05	3.35	5.94	0.77-45.92
Von Doersten et al[21]	104	0.36	0.51	6.09	−1.37	0.80	0.36- 1.77
Woolley et al	143	0.46	0.69	7.62	8.31	3.20	1.48- 6.93
Total or average	741	0.36	0.63	33.16	32.79	2.65	1.88- 3.72

Recur — rate of recurrence, Trans — rate of transfusion of any amount of blood products, Var — variance for each study calculated from Mantel-Haenszel[23] formula, O–E — observed minus expected number of cases, OR — odds ratio calculated from logistic regression, 95% CI — lower and upper boundaries of confidence interval calculated from logistic regression coefficients and standard error of coefficient.

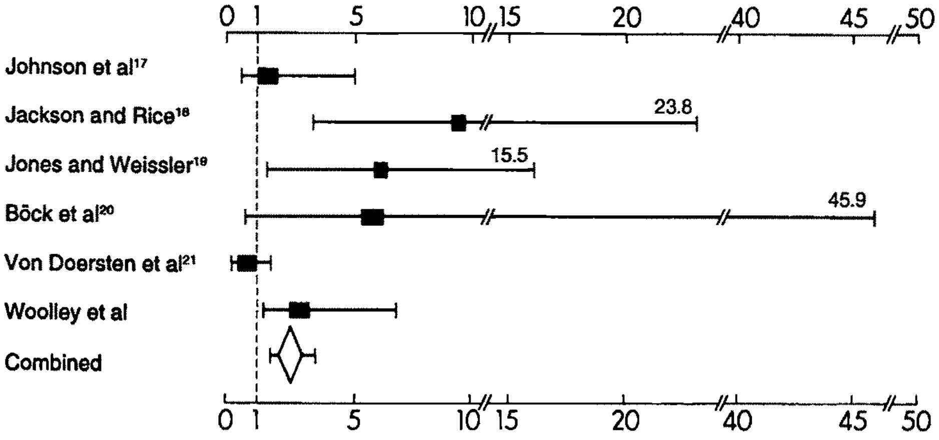

Fig 3. Odds ratios for each study are noted in each row. Filled square represents odds ratio of recurrence for any blood products, along with 95% confidence intervals. Unfilled diamond indicates composite odds ratio (see text for calculation details) for all six studies. Size of symbol is proportional to number of subjects in each study. Those studies with lower boundary of 95% confidence interval of less than 1 are considered to be not significant at $p = .05$. Odds ratio of 1 indicates no effect from transfusion.

pression. Transfusions have been found to increase T cell suppressor activity for at least 12 weeks following transfusion.[30] Fischer et al[31] found a measurable effect from a single transfusion, but with a second transfusion there was a more pronounced and prolonged state of immunosuppression. Transfusion with autologous blood causes no immunosuppression. Tartter et al[32] noted significant reductions in total number of T cells in transfused patients measured at 6 to 18 months after transfusion. This was directly proportional to the number of units of blood transfused perioperatively. Natural killer cells are thought to play a role in controlling oncologic disease.[33] Natural killer cell activity is significantly depressed immediately following transfusion. This effect has also been shown to be dose-related and may be prolonged as long as 3 months.[34] An increase in serum levels of prostaglandin E, a potent immunosuppressant, has been documented in patients receiving blood transfusions, and this effect is also dose-dependent.[35]

Several clinical studies have examined the effect of blood transfusion on cancer recurrence since Burrows and Tartter[6] in 1982 indicated an increased recurrence rate in patients with colorectal carcinoma who received blood transfusions. Similar associations have been reported in patients with lung cancer,[11,12] breast,[12] renal cell,[14] and head and neck carcinomas, as well as soft tissue sarcomas.[13] Not all investigators, however, have found an adverse relationship between transfusion and cancer recurrence.[15,16,20,21] Of the five reports on head and neck cancer patients, three[17-19] supported the relation of blood transfusion to recurrence and two did not.[20,21]

Johnson et al[17] retrospectively analyzed the outcomes of 139 patients with stage III squamous cell carcinoma of multiple sites in the head and neck and identified a significantly increased recurrence rate in those patients who received 3 units or more of blood products compared with those receiving 0 to 2 units. This difference was absent in those patients treated by surgery alone or after failed radiotherapy. Using their data for all 139 cases, we computed an odds ratio for recurrence after any transfusion of 1.86 and found a 95% CI of 0.68 to 5.08 (Table 3).

Jackson and Rice's review[18] of 100 patients with squamous cell carcinoma of the head and neck showed a significantly increased risk of recurrence in those patients who had received blood products. A higher rate of recurrence was found in patients with oral cavity, pharynx, nose, or paranasal sinus carcinoma compared to those patients with laryngeal cancer. Their analysis, which was stratified by tumor stages I through IV, showed no effect of stage on the relation of transfusion status to tumor recurrence. Ninety percent of cases were stage II or higher. Their odds ratio (95% CI) was 9.40 (3.70 to 23.80).

Jones and Weissler[19] performed a multivariate analysis of blood transfusion and 15 other prognostic variables using recurrence as the dependent variable in 94 cases of stage III to IV cancer of the head and neck. Margin status and blood transfusion were found to be significant predictors of recurrence. Their odds ratio (95% CI) was 6.18 (2.86 to 15.50).

Böck et al[20] studied 161 patients with stage I to IV cancer of the larynx with a median follow-up of 42 months. Patients who received blood transfusions were found to have a higher incidence of recurrence, but when they were analyzed separately within nodal status, histologic grading, or stage, no significant difference was detected. Recurrence was related to stage, lymph node status, and histologic grading. All patients had a total laryngectomy as their primary surgical treatment. Included were 22 patients with stage I and 58 stage II tumors undergoing total laryngectomy. Their overall recurrence rate of 16.7%, which was less than half that of the other studies, probably reflects the large number of stage I and II cases, which had 4.5% and 5.8% recurrence rates, respectively. Of interest, their transfusion rate was nearly double the average transfusion rate of the other studies. Their odds ratio (95% CI) of 5.94 (0.77 to 45.92) indicates a high variance and a nonsignificant ($p = .089$) main effect of transfusion on recurrence.

Von Doersten et al[21] analyzed 31 clinical variables from 104 cases of stage II through IV head and neck cancer at multiple sites. They excluded all cases with positive margins and preoperative radiotherapy. Their multivariate analysis indicated that age, nodal status, and postoperative hematocrit were significant predictors of recurrence. Transfusion status was not significant for recurrence in either the multivariate analysis or the univariate analyses. Interestingly, transfusion status was a significant predictor of infection in the univariate analysis, but not in the multivariate analysis. Multiple head and neck sites were included. They, as we, found that metastatic node status was the strongest predictor of recurrence, more so than clinical N staging. Their odds ratio (95% CI) was 0.80 (0.36 to 1.77), which clearly indicates that transfusion did not adversely affect tumor recurrence in their cases.

The variations in experimental design among these studies create uncertainty about which studies are correct. Therefore, we employed the technique of meta-analysis, which permits all available studies to be combined for the purpose of estimating an overall effect. The validity of meta-analysis depends in part on the quality of the studies and avoidance of bias from unpublished studies, which often are negative.[36] We believe that this meta-analysis has incorporated all published studies: 4 positive (including this one) and 2 negative. Although there may be unpublished negative studies, it would take 25 studies of similar design and sample size with odds ratios of 1 to negate the overall effect demonstrated here. Therefore, we may conclude that a publication bias is unlikely to exist.

The current meta-analysis examines only the main effect of transfusion status on recurrence rate, and this is substantial. (To do a more sophisticated multivariate analysis would require pooling of the raw data.) The finding of a significant main effect of blood transfusion on recurrence of head and neck cancer in this meta-analysis supports the current theory that transfusion predisposes to tumor recurrence. Until this theory is rejected or modified by further investigation, it would be prudent to use techniques for blood conservation.[37,38] By this we mean enhanced hemostasis using electrocautery dissection and, where possible, the argon beam coagulator, intraoperative hemodilution, use of autologous transfusion (where applicable), and the judicious use of heterologous blood products, in particular those that minimize the transfer of leukocytes. Further research into the mechanism of the transfusion effect and methods to reduce its impact is warranted.

It appears to us that the transfusion effect is most evident in high-risk cases in which the immune system is already stressed by poor nutrition, large tumor burden, and prolonged operative and anesthesia time. It may be the case that in these circumstances, transfusion adds an additional stress to the immunologic system. If that is indeed the case — and we believe the information in this review points strongly in that direction — we as head and neck surgeons already have at our disposal the means, by careful attention to blood conservation, to reduce that burden and thus potentially enhance our patients' survival.

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PHONATION AND SWALLOWING CONSIDERATIONS IN PEDIATRIC LARYNGOTRACHEAL RECONSTRUCTION

MARSHALL E. SMITH, MD
DENVER, COLORADO
ROBIN T. COTTON, MD
CINCINNATI, OHIO

ANTHONY J. MORTELLITI, MD
VALHALLA, NEW YORK
CHARLES M. MYER III, MD
CINCINNATI, OHIO

Experience with laryngotracheal reconstruction (LTR) has resulted in and continues to yield modifications and refinements in approach and technique with the goal to restore and maintain total laryngeal function. In addition to airway obstruction, the laryngeal functions of phonation and swallowing also may be affected by the underlying injury as well as by procedures designed to enlarge the airway. This paper discusses various problems encountered with phonation and swallowing in pediatric patients who underwent LTR and postoperative patients who were seen during the year July 1, 1990, through June 30, 1991. Phonation problems became apparent as long-term difficulties that persisted after tracheotomy decannulation. Swallowing was frequently a short-term perioperative problem while a stent was in place following LTR. The approaches and techniques that have been employed to treat, minimize, and prevent these problems are discussed.

KEY WORDS — laryngotracheal reconstruction, laryngotracheal stenosis, phonation, swallowing, voice.

INTRODUCTION

Surgical therapy of laryngotracheal stenosis has made many advances. Laryngotracheal reconstruction (LTR) aims to enlarge the lumen of the airway and permit tracheostomy decannulation. Good success has been reported with a variety of techniques.[1-4] Further advances in laryngeal surgery have come about with conservation laryngeal surgery for laryngeal carcinoma[5] and external framework laryngeal surgery (thyroplasty) in the treatment of glottic insufficiency and vocal pitch disorders.[6] Implicit in the application of these techniques is a recognition of the threefold function of the larynx — airway, phonation, and swallowing. Laryngeal surgery designed to address one aspect of laryngeal function may necessarily affect the other functions of the larynx.

The primary goal of LTR surgery is improving the airway. Tracheostomy decannulation has been a high priority in infants and children because of the relatively high morbidity and mortality associated with pediatric tracheostomy.[7] Another impetus for tracheostomy decannulation in children is to aid in development of speech and language. The presence of a tracheostomy impairs speech development if the tracheostomy is present for lengthy periods extending into the linguistic stage.[8] Phonation in the child with a tracheostomy is impaired by the diversion of airflow from the larynx and the underlying stenosis of the subglottic or tracheal lumen. In severe cases, this results in total obstruction of laryngeal airflow with resulting aphonia. As these children are operated on, decannulated, and followed up in the long term, the effects of laryngotracheal stenosis and the procedures used to treat it can be evaluated for their effect on global laryngeal function, including phonation and swallowing.

Phonation following pediatric LTR has been assessed in limited retrospective reviews by several authors. Zalzal,[9] in a study of the treatment of posterior laryngeal stenosis in a small series of patients, surveyed the voice quality as assessed by the household member who spent the most time with the patient before and after surgery. Of the 8 patients with preoperative normal voice quality, only 2 had a postoperative normal voice quality, with 6 patients reported as having a hoarse or husky voice quality. Voice intelligibility improved in 4 patients, worsened in 2, and did not change in 3. Maddalozzo and Holinger[10] reported in a series of 20 children who underwent LTR that hoarseness was not an infrequent problem in those who required stenting. Cotton[11] reported on 61 patients who underwent LTR with posterior or anterior and posterior costal cartilage grafts. Because patients frequently lived far from the center in which reconstruction was per-

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From the Department of Otolaryngology–Head and Neck Surgery, The Children's Hospital and University of Colorado Health Sciences Center, Denver, Colorado (Smith), the Department of Otolaryngology–Head and Neck Surgery, Westchester County Medical Center, Valhalla, New York (Mortelliti), and the Children's Hospital Medical Center and University of Cincinnati School of Medicine, Cincinnati, Ohio (Cotton, Myer).

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REPRINTS — Robin T. Cotton, MD, Dept of Otolaryngology, Children's Hospital Medical Center, Elland and Bethesda Avenues, Cincinnati, OH 45229.

P24725

formed, quality of voice or cry was assessed by a survey of the patient or parent in a manner similar to that of Zalzal.[9] The subjective assessment was that in 3 cases the voice was felt to have been made worse. In 23, there was no difference in the voice, and in 35 the voice quality had improved. The duration of stenting was found to be correlated with postoperative voice assessment, in that better voice results occurred when the duration of stenting was 12 weeks or less.

There are few objective studies of voice problems following pediatric LTR, but those available provide a more detailed view of the problem. They include perceptual studies, acoustic analysis, and fiberoptic laryngoscopic examination. Sell and MacCurtain[12] reported on the speech and language development in 16 children with subglottic stenosis who underwent LTR. Their perceptual evaluation categorized only 31% with an acceptable voice, 38% with a moderately abnormal voice, and 31% with a severely abnormal voice. The vocal pitch was usually low, with a rough and breathy quality. In the same group of patients, Kearns et al[13] reported fiberoptic nasopharyngolaryngoscopy findings of anterior commissure blunting, false vocal fold phonation, anterior overfolding of the arytenoids, and poor or limited movement of one or both arytenoids. Zalzal et al[14] studied the post-LTR voice quality using perceptual rating scales and multiple listener assessment in 16 patients who underwent LTR and decannulation. Fifteen of the 16 patients had aberrant voice quality, characterized by low pitch and breathy and hoarse voice. Smith et al[15] studied 8 patients with perceptual ratings and acoustic measures, as well as videolaryngostroboscopy. The voices were characterized by low pitch, diminished pitch range, decreased intensity, and shortened phonation time compared with age- and sex-related norms. Reverse (inhalational) phonation was observed in 3 patients, and 3 patients used supraglottal constriction to phonate. Laryngoscopy and laryngostroboscopy demonstrated severe glottic incompetence in 2 patients, vocal fold asymmetry in stiffness and/or position (eg, absence of mucosal wave, vocal folds on different levels) in 3 patients, and phonation using supraglottic structures in 3 patients. These reports are the first to document phonation problems encountered in pediatric LTR patients and underscore the need for attention in this area.

It has been our impression also from long-term follow-up that voice and resultant speech quality and intelligibility have been a problem for some patients, with impairment of ability to communicate at school and in social interactions. This becomes more of an issue as children develop linguistically and enter the social environment. Although assessment of long-term objective outcomes is not yet possible, we felt it important to address this issue, realizing that the outcome of LTR performed on young children may have effects in terms of phonation that may only become apparent years later.

Swallowing problems in pediatric LTR have been seen as a problem associated with the endolaryngeal stent. Maddalozzo and Holinger[10] reported in their series that transient aspiration was commonly seen for 2 to 4 days following stent removal. Gray et al[16] found that some degree of dysphagia and aspiration was seen universally after LTR in the early postoperative period, related mainly to the presence of a stent. This lasted usually for 7 to 10 days. In the long term, swallowing problems have not been seen generally, as reported by Zalzal[9] in his series of posterior cricoid cartilage grafts. The observation of phonation and swallowing disorders following LTR prompted us to review our experience in this regard. Modifications and changes in our approach that aim to prevent or minimize these problems are discussed.

METHODS

A review was conducted of the operative experience of LTR for the year July 1, 1990, to June 30, 1991. Sixty-three LTR procedures (37 primary and 26 revision) were performed on 56 patients; 38 were boys and 18 were girls. Five patients underwent 2 LTR procedures, and 1 patient underwent 3 LTR procedures during this period. Ages ranged from 4 months to 19 years. Twenty-nine (51%) of the patients were 3 years of age or younger. Excluded from this series were 7 tracheal reconstructions, since swallowing and phonation problems were not seen in these patients. The procedures all were performed at the Children's Hospital Medical Center, Cincinnati, Ohio. Follow-up visits and endoscopy also were conducted on patients who previously underwent LTR at this institution. Speech pathology referral was made routinely. Phonation results were assessed comprehensively in 2 patients in the study group, as well as 6 others who were decannulated prior to the study period.[15] These patients were selected because of dysphonias manifest following extubation or decannulation in children age 4 or older who could cooperate for examination. On the basis of experience in care for these patients, aspects of phonation and swallowing were reviewed specifically.

RESULTS

A summary of the procedures performed is given in Table 1. Cartilage grafts were used in 50 cases. The stent types are listed in Table 2, along with average

TABLE 1. TYPES OF PROCEDURES

Procedure	*No. of Cases*
Anterior graft	21
Posterior graft	19
Anterior and posterior graft	8
Anterior split	3
Anterior and posterior split	8
Anterior and posterior split and anterior graft	2
Four-quadrant split	5
Partial cricoid resection	2

Cartilage grafts in all cases were autogenous costal cartilage, except for auricular cartilage used in four cases. In some cases, more than one procedure was employed, eg, four-quadrant split and posterior graft.

stenting duration. The split procedures, without grafting, in nearly all cases were done in combination with placement of a "wired in" stent or Montgomery T-tube. The above-stoma stent was associated with placement of a cartilage graft in 27 of 29 cases.

Phonation. Prior to LTR, phonation problems were anticipated in 16 patients. Fifteen of these had undergone prior LTR. Findings included stenosis and scarring involving the vocal folds, arytenoid fixation, and anterior commissure disruption. In 2 previously operated cases referred from other institutions for evaluation during this study period, prior placement of an anterior cartilage graft in the middle or superior portion of the thyroid cartilage resulted in wide displacement of the vocal folds, with severe distraction of the anterior commissure and resultant marked glottic insufficiency (Fig 1).

In two cases during LTR, a stent modification was employed to minimize phonation problems. In both patients, the airway disorder involved an anterior subglottic stenosis with no involvement of the membranous vocal folds or their undersurface. A stent was deemed necessary to stabilize an anterior cartilage graft. Rather than the Teflon Aboulker stent, a silicone cylinder cut from the limb of a Montgomery T-tube was used. It was placed with the superior edge of the stent no higher than the upper edge of the anterior rim of the cricoid or lower cricothyroid membrane. This placement limited formation of granulation tissue on the undersurface of the vocal folds in the tapered subglottic region (Fig 2). The stent was left in place for 6 weeks. Phonation results following stent removal were excellent in both cases. A Montgomery T-tube with the upper limb placed below the vocal folds in the subglottis was similarly used in two cases.

TABLE 2. STENT TYPES USED AND AVERAGE STENT DURATION

Stent Types		*No. of Cases*	*Average Stent Duration*
Above-stoma stent		29	6 wk
Aboulker	25		
Portex tube	2		
Silicone tube	2		
Endotracheal tube (single-stage LTR)		15	10 d
Wired-in stent, tracheal complex		9	3 mo
No stent		5	
Montgomery T-tube		4	8 mo
Upper limb below vocal folds	2		
Upper limb above vocal folds	2		

LTR — laryngotracheal reconstruction.

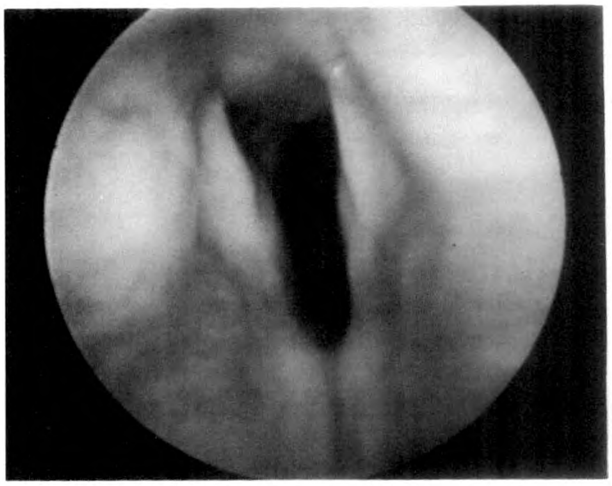

Fig 1. Placement of cartilage graft into anterior commissure of larynx, widely distracting vocal folds with resulting glottic incompetence. Breathy, weak voice would result. Graft placement below this level, if possible, is recommended.

During the study period, patients who underwent single-stage LTR underwent perceptual voice assessment 3 to 6 months postoperatively. This provided a

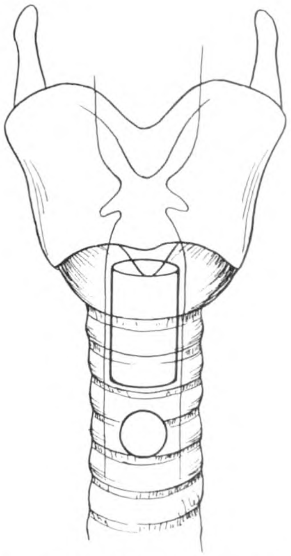

Fig 2. Stent placement below vocal folds in subglottis may be useful in selected cases. This avoids stent pressure against vocal fold mucosa.

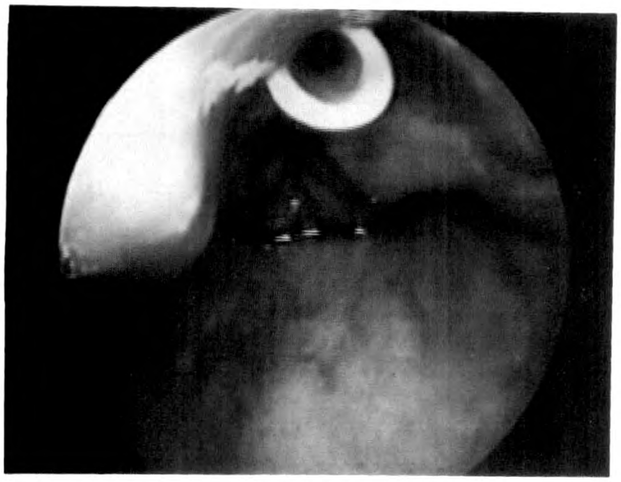

Fig 3. Long-term endolaryngeal stent made of blue-line Portex endotracheal tube with beveled edge facing epiglottis, to prevent aspiration.

group comparable in terms of similar LTR procedure type, whose voice was evaluable within the study period. Fifteen patients underwent single-stage LTR with endotracheal tube stenting. There were 10 primary and 5 revision procedures. Nine had anterior cartilage grafts, 5 had combined anterior-posterior cartilage grafts, and 1 had a posterior cricoid cartilage graft only. Twelve patients were successfully extubated. Nine of 11 patients with a preoperative tracheostomy were decannulated. Seven patients had normal phonation following single-stage LTR. Four patients exhibited a moderate degree of dysphonia, but were too young for objective voice assessment. One patient had a severely abnormal voice postoperatively. This patient had severe laryngotracheal stenosis involving the glottis, had abnormal phonation preoperatively, and had undergone prior LTR procedures. All 5 of the patients with moderately or severely abnormal voices had both anterior and posterior cartilage grafts placed at LTR. In 3 of these 5 patients the single-stage LTR was revision surgery.

Two patients in the study group with phonation problems after LTR underwent objective voice assessment. Both patients had undergone revision LTR procedures. One exhibited severe glottic insufficiency, and the other patient had dysphonia related to vocal fold asymmetry and anterior commissure blunting. Their case histories and voice findings are reported elsewhere as part of a larger group of patients.[15] Further voice studies of the patients decannulated during this study period are under way.

Swallowing. Swallowing outcome was assessed by average post-LTR hospital stay in those patients who required long-term stents. Those patients who underwent single-stage LTR (endotracheal tube) or LTR without stenting did not have postoperative swallowing difficulties. The average hospital stay for patients with above-stoma stents was 6 days, and for those with "wired-in" full-length stents it was 8.5 days.

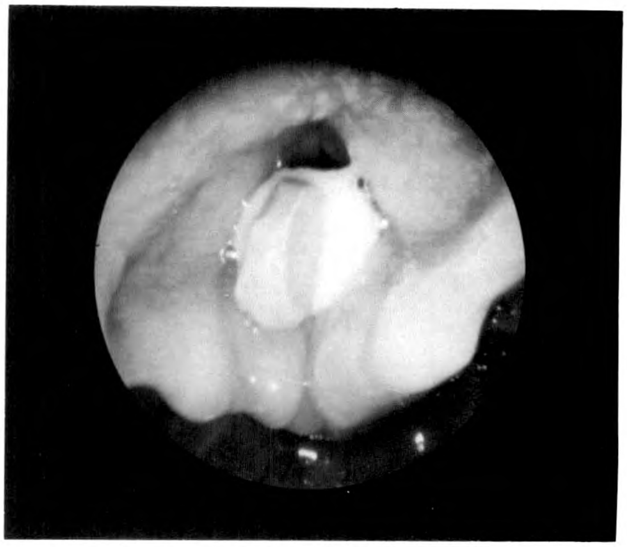

Fig 4. Temporary plug in hole at top of Aboulker Teflon stent to prevent aspiration during stenting time.

When swallowing difficulties were anticipated preoperatively, yet a stent was required for LTR, several techniques were used. The removable capped end of the Aboulker stent was sewn with nonabsorbable suture to the stent and used in this fashion. In two cases, a stent with the upper end below the vocal folds in the subglottis was used. In two cases, a stent made of a blue-line Portex endotracheal tube was used (Fig 3). It was placed with the beveled edge facing the laryngeal surface of the epiglottis. It worked well in both cases to prevent swallowing difficulties in these patients who required a long-term endolaryngeal stent.

In two patients, severe aspiration through the hole in the Aboulker stent was not ameliorated by diet manipulation. In these cases, early removal of the stent was felt to compromise the LTR result. Therefore, a plug was devised and molded of dental impression silicone (vinyl polysiloxane, Imprint, 3M Co, St Paul, Minn). With the patient briefly under a general anesthetic, it was placed endoscopically under direct vision into the hole at the top of the stent (Fig 4). The aspiration difficulties resolved immediately in each case.

For gastroesophageal reflux uncontrolled on medical management, in one case a Nissen fundoplication was required prior to consideration for LTR surgery. If a gastrostomy tube was present, it was used for feedings during the stenting period. No patient was readmitted for pneumonia during their stenting period, although many required one or more courses of oral antibiotics for purulent secretions while the stent was in place.

DISCUSSION

Phonation. Phonation is often a secondary consideration in the young infant or child with laryngotracheal stenosis and a tracheostomy. The primary focus for parents and physician alike is the airway. Ability to assess phonation is complicated by the developmental age of the child, the presence of a tracheostomy, and the variability of the airway disorder. Frequently these patients are prelinguistic or early in language development. They may be rendered aphonic by the stenotic lesion itself. These factors make it difficult to determine the incidence of phonation problems in children following LTR. Zalzal et al[14] felt that the abnormal voice quality in children after LTR is from the original laryngeal injury and is compounded by surgery to correct the stenosis. What requires attention is the extent to which the airway disorder and reconstructive surgery contribute to the final voice result in the individual patient. The aspects that may be controlled — the preoperative evaluation and LTR surgical options — are those that may affect the outcome of the voice long after the patient has been decannulated.

In the preoperative evaluation, vocal cord mobility is evaluated carefully, especially with posterior glottic stenosis. We use laryngeal electromyography (EMG), applying the technique reported by Koch et al,[17] on occasion to ascertain laryngeal neuromuscular function. Arytenoid position and mobility are carefully examined, as well as the glottic extent of the stenosis itself. Severe laryngeal stenosis that involves the free margin of the true vocal folds (fused vocal folds) will adversely affect phonation regardless of other considerations. The parents should be counseled preoperatively that in the long term the voice may not be normal. If the free margins of the membranous folds are uninvolved, every effort may then be taken to protect them.

At the time of LTR, special attention to several anatomic structures of the larynx that affect phonation may influence the postoperative voice result. These include the anterior commissure, the vocal fold mucosa, the laryngeal nerves, and the arytenoids.

Problems with the anterior commissure have affected the postoperative voice result.[13,15] The anterior commissure and the level of the free margin of the vocal folds is at the midpoint between the thyroid notch and the inferior edge of the thyroid lamina in children.[18] It is advantageous to avoid a complete laryngofissure through the anterior commissure when possible. If possible, the superior extent of the incision should extend no higher than one third the anterior height of the thyroid lamina. Despite descriptions from previous reports,[9,19] complete laryngofissure often was not required in our experience in order to perform a posterior cricoid division, or to place a posterior cartilage graft. When complete laryngofissure was necessary, exact reapproximation of the anterior commissure was found to be crucial to avoid glottic problems at this level. This was aided by marking the midline with methylene blue prior to division. We have observed both blunting of the anterior commissure and vocal folds at different levels, with resultant vertical asymmetry in vibration of the vocal folds following LTR surgery.[15] This has affected adversely the postoperative voice result.

When an anterior cartilage graft is employed in LTR, it is important to avoid placing the superior end of the cartilage graft into the middle of the thyroid cartilage, as was seen in several patients referred to our institution. The superior portion of the graft should extend if possible just to the inferior edge of the thyroid lamina. Placement of the anterior cartilage graft in the cricothyroid membrane, between the cricoid and thyroid cartilages, likely affects the function of the cricothyroid muscle. The action of this muscle, by drawing the two cartilages together anteriorly while the larynx rotates on the cricothyroid joints, results in a stretching and thinning of the vocal folds, causing elevation in pitch during phonation. Some limitation in pitch range might be expected in post-LTR patients with an anterior graft. Pitch limitation may manifest when the child is older and attempts to sing. This question requires further long-term investigation.

Complete anterior laryngofissure also can result in the posterior displacement of the petiole region of the epiglottis, with blunting of the anterior commissure and foreshortening of the anterior-posterior dimension of the supraglottis at or above the false vocal folds. This postoperative configuration was sometimes seen in patients who required multiple LTR procedures.[1] We hypothesize that repeated complete laryngofissure disrupts the suspension of the epiglottis at the thyroepiglottic ligament and yields fibrosis in the preepiglottic space.

The vocal fold mucosa is a freely pliable membrane when uninvolved with the stenotic process. It vibrates through interaction with the subglottic airstream and underlying contraction of laryngeal muscles to produce the acoustic source for the vocal tract. The development of scar in the lamina propria of the vocal fold will inhibit vibration and impair the postoperative voice. Therefore, it is important to

TABLE 3. POTENTIAL ADVERSE EFFECTS ON PHONATION AND TECHNIQUES USED TO AVOID THEM

Procedures	*Potential Adverse Effects on Phonation*	*Techniques*
Anterior laryngotracheal split and/or graft	Anterior commissure disruption; vocal fold vertical asymmetry; cricothyroid muscle dysfunction; supraglottic collapse	Avoid complete laryngofissure, if possible; avoid graft placement in anterior commissure; perform exact alignment of anterior commissure
Posterior laryngotracheal split and/or graft	Increased glottic gap; impaired arytenoid adduction; arytenoid subluxation	Avoid excessive graft width; use gentle retraction of hemicricoid
Four-quadrant split	Recurrent laryngeal nerve injury	Use hemicricoid division at midportion or anteriorly
Stents	Scarring of vocal fold mucosa; impaired arytenoid mobility	Minimize stenting time; use single-stage laryngotracheal reconstruction, if possible; stent below vocal folds, if possible

avoid trauma to the vocal fold mucosa during LTR. One possible source of trauma is the endolaryngeal stent. The stent, although lying mainly in the posterior glottis and abutting the vocal processes of the arytenoids, also may contact the free edge of the anterior vocal folds. This prolonged endolaryngeal intubation may result in vocal fold scar formation.

In a goat animal study of the effect of long-term endolaryngeal stents on the larynx, disruption of laryngeal mucosa and the underlying tunica elastica, particularly in the posterior glottis, was observed in preparations that underwent endolaryngeal stent placement for 3 months.[20] Squamous metaplasia of the posterior glottic mucosa was seen, as well as erosion of the vocal process. Epithelial hyperplasia and fibrous proliferation in the submucosa anterior to the vocal process were observed. Leonard et al[21] studied the effect of 7-day intubation in small dogs. Larynges harvested 5 weeks after extubation exhibited epithelial disruption, hypertrophy of the epithelial layer, and proliferation of subepithelial connective tissue. These changes, although mainly in the posterior glottis, also were observed in the membranous fold anterior to the vocal process. The implications of these animal studies point to adverse effects on phonation from endolaryngeal stents.

In planning LTR surgery, we have found it helpful to minimize the stenting time to spare injury to the vocal fold mucosa. In selected cases, when the stenotic process was confined to the subglottis and not involving the free edge of the vocal folds, and stent placement was deemed necessary to stabilize the graft, a stent was placed below the vocal fold mucosa. The single-stage LTR also has advantages in regard to minimizing vocal fold injury. In our experience, phonation results generally have been good when this technique, with its short stenting period, has been used.

Injury to the laryngeal nerves must be avoided in order to optimize postoperative phonation. The external branch of the superior laryngeal nerve innervates the cricothyroid muscle. Electrocautery around the cricoid or on the cricothyroid muscle may injure this nerve and cause a superior laryngeal nerve paralysis. While not having a marked effect on postoperative voice quality, it may affect it to some degree, to limit pitch range and singing. More important is avoidance of injury to the recurrent laryngeal nerve. Anterior and posterior laryngotracheofissure is kept in the midline, away from the tracheoesophageal groove. When four-quadrant cricoid division (lateral cricoid cuts) is employed, it is important to stay anterior on the hemicricoid to avoid injury to the recurrent laryngeal nerve.[22]

The arytenoid cartilages also affect postoperative phonation ability. It is important to assess arytenoid position and mobility preoperatively. During surgery, excessive retraction on the hemicricoid during the placement of posterior grafts may subluxate or dislocate the arytenoid cartilage. This would affect vocal fold mobility as well as airway patency. Cricoarytenoid joint fixation was seen following LTR in several patients with breathy voices studied by fiberoptic laryngoscopy.[15] These patients had required long-term stenting and multiple procedures.

A summary of phonation problems, their relation to LTR procedure types, and suggested technical details is provided in Table 3.

In the interpretation of reports of voice quality and phonation following LTR it is important to recognize several factors. Apparent satisfaction with the outcome of LTR surgery in terms of voice may reflect parent satisfaction that the tracheostomy is no longer present and that the child is better able to communicate without a tracheostomy, especially if the child was aphonic preoperatively. This is reflected in the survey of Sell and MacCurtain,[12] in which the parents of 16 patients after LTR surgery were questioned to detect the parental degree of satisfaction with residual voice quality after decannulation. Ninety-three percent classified the speech as different from that of other children. Fifty percent were happy with the

TABLE 4. AVOIDANCE OF SWALLOWING PROBLEMS

TABLE 4. AVOIDANCE OF SWALLOWING PROBLEMS
Assess swallowing difficulties preoperatively, especially in neurologically delayed children
For posterior cricoid split, avoid complete division of interarytenoid muscle
Use gastrostomy tube, if present, during stenting time
Minimize stenting time
Use single-stage laryngotracheal reconstruction, when possible
Stent below vocal folds, when possible
Advance feedings slowly
Thicken feedings
When Aboulker stent used, plug or cap hole if necessary
When long-term stent needed, try beveled Portex endotracheal tube

voice and 46% classified the voice as a problem. Despite this, 80% of parents stated they would proceed with surgery again for their child despite the resultant voice.

The quality of the post-LTR pattern of abnormal phonation has been compared to the voice of adults who have undergone partial laryngectomy.[14] This type of voice likely becomes a long-term physical disability for a child. Disordered voices adversely affect peers' and adults' perceptions of certain physical and personality traits of children.[23,24] Long-term education and employment opportunities are likely to be affected. The longer the patients have been followed up after LTR, the more voice has become an issue of concern for parent and patient. Clearly, long-term prospective studies are needed to evaluate further subglottic and laryngeal stenosis, its treatment with LTR, and the resulting effects on voice.

Swallowing. In the study period, swallowing difficulties manifested as a perioperative problem during the stenting time following LTR. When the stent was placed through the larynx to rest at the level of the arytenoids and epiglottis,[25] aspiration occasionally developed through the hole in the top of the stent. Prolonged aspiration, even when low-grade, manifested during the stenting time as recurrent cough, tracheobronchitis, or pneumonia. These were treated with oral antibiotics. No patient required hospitalization for these problems during the study period. Patients with swallowing difficulties also had poor weight gain during the stenting period.

The preoperative assessment of swallowing is an important part of the evaluation in children who undergo LTR. Children with tracheostomies and laryngotracheal stenosis due to prolonged intubation as premature neonates frequently exhibit feeding difficulties. Poor sucking ability, hypotonic or hypertonic reflexes, behavioral feeding problems, and alterations in anatomy of the upper aerodigestive tract place them at risk.[26] These children also are more prone to develop gastroesophageal reflux. A thorough feeding history is taken to ascertain the presence of swallowing difficulties. An esophageal pH probe and a radionuclide gastric emptying scan are performed to check for gastroesophageal reflux.

Assessment of the preoperative risk of aspiration is important in planning the type of LTR procedure, the design of the stent, and the stenting duration. Following the LTR surgery, diet was advanced slowly. Most patients with an intralaryngeal stent exhibited aspiration to some degree initially. The use of soft or pureed diet and food thickeners was helpful in the first 7 to 10 days postoperatively in improving swallowing and was occasionally required during the entire stent duration.

Those patients with posterior cricoid splits and grafts tended to have more postoperative swallowing difficulties. This was particularly evident in those with developmental delay. It was important in the posterior cricoid split to avoid complete division of the interarytenoid muscle, which could impair glottic closure during swallowing.

Following stent removal, most swallowing problems resolved quickly. Posterior cricoid splits and grafts theoretically increase the risk of long-term aspiration. This has been observed to be a long-term problem in a few patients with preoperatively identified feeding problems. Those with feeding difficulties before LTR, whose therapy was interrupted by LTR and stenting, required close follow-up and reinstitution of therapy. A summary of recommendations to avoid swallowing problems following LTR is given in Table 4.

CONCLUSION

As important functions of the larynx, swallowing and phonation are affected by LTR surgery. Impairment of swallowing is usually a perioperative problem during the time of endolaryngeal stent placement. Premature, neurologically impaired, and developmentally delayed children have an increased risk of swallowing difficulties as well as gastroesophageal reflux. It is important to assess the preoperative risk of swallowing problems and aspiration in planning the type of procedure and the stenting duration. Diet manipulation in the postoperative period is frequently needed to aid swallowing and to prevent aspiration. Stent plugs or stents placed below the vocal folds may be helpful in selected cases to minimize perioperative swallowing difficulties. It is apparent that swallowing difficulties also may be ameliorated with shorter stenting duration, or use of techniques that avoid stent placement, such as single-stage LTR.[27]

Impairment of phonation is usually a delayed postoperative problem, most apparent after decannulation. If the stenotic lesion involves the free edges of the vocal folds or the posterior glottis, phonation difficulties may be anticipated. Attention to surgical details during LTR surgery may prevent or minimize phonation difficulties and yield a satisfactory long-term result. Concomitant speech and language delays and disabilities are seen frequently in these patients. Close follow-up and speech-language therapy often are required to enhance the child's communicative skills. Prospective studies of vocal function with long-term follow-up in pediatric LTR patients are advocated for further investigation of these problems.

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Ann Otol Rhinol Laryngol 101:1992

CONSUMER PRODUCT ASPIRATION AND INGESTION IN CHILDREN: ANALYSIS OF EMERGENCY ROOM REPORTS TO THE NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM

JAMES S. REILLY, MD MARGARET A. WALTER, MD

BIRMINGHAM, ALABAMA

Inadvertent aspiration or ingestion of products in children is a reportable problem. The National Electronic Injury Surveillance System (NEISS) monitors 119 hospitals for product (nonfood) hazards through a network of emergency room physicians. Coins (52%) remain the most frequently ingested object (1988-1989). Pins, including nails and bolts, are second in rank. Spheres (eg, balls) are the most common cause of death. Most deaths (97%) occur in the home. Younger children (13.4 versus 22.7 months) are more at risk for death. This analysis suggests that shape, as well as availability, is important in children's injuries and deaths. Accurate reporting to NEISS of all aspirated objects remains essential so that product safety and the public's health can be improved. Food product injuries, however, are not reported to NEISS.

KEY WORDS — aspiration, foreign body, ingestion, National Electronic Injury Surveillance System.

INTRODUCTION

Aspiration or ingestion of a foreign object (FB/AI) remains a persistent and occasionally fatal problem. Morbidity and mortality figures have improved dramatically through the employment of hospital-based benefits such as improved bronchoscopic removal techniques, as well as the safer use of general anesthesia. Recent efforts have focused on improved public health safety measures such as outreach programs of prevention and education to prevent children from gaining access to small objects.

The Consumer Product Safety Commission (CPSC) developed in 1973 the National Electronic Injury Surveillance System (NEISS), which monitors product-related injuries through an integrated system of 119 hospitals and/or their emergency physicians.[1] This network of hospitals was designed to represent all US geographic regions and collect important data that are disseminated through government agencies to the public.

Judgment on public health issues, such as the Small Parts Test Fixture, is based on these figures.[2] The data are also important because they monitor changing trends of injury and identify newer hazardous products. The NEISS system is unique, and it provides to the physician data on events that occur in the home or work place and are brought to the emergency room. The sensitivity of this reporting system for identifying offending objects is untested, but it remains the benchmark for decisions on public health issues.[3]

Bronchoesophagologists are quite familiar with the persistent, severe FB/AI injuries that require hospitalization. Physicians may be less familiar with choking events that occur in the home and are screened and evaluated by emergency physicians. Our ability to assist in prevention of FB/AI injuries and to conduct education programs for childhood safety requires that we be equally familiar with this other, largely outpatient data base.

Therefore, we undertook a retrospective analysis of NEISS data (1988 through 1990) to assess the present risk of FB/AI mortality and/or morbidity from common household and everyday objects.[4] A better awareness of these data is particularly important to physicians who are responsible for the evaluation and surgical removal of persistent foreign bodies.

These data are important to improving childhood safety, particularly at home. Careful scrutiny is important to understanding the mechanism and frequency of aspiration of persistent foreign bodies.

MATERIALS AND METHOD

Data from the CPSC computers were obtained for the years 1988 through 1990. The NEISS system is a federally funded arm of the CPSC. This data retrieval network possesses the ability to monitor approximately 119 hospitals throughout the United States. An outpatient record is completed that includes the date of the accident, case number, sex and age of the victim, diagnosis and body part affected, disposition,

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From the Department of Surgery, Division of Otolaryngology–Head and Neck and Neck Surgery, University of Alabama at Birmingham, Birmingham, Alabama.

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FOREIGN BODY ASPIRATIONS AND INGESTIONS

		Boys		*Girls*		*Mean Age*	*% Aspi-*	*% At*
	Total	*No.*	*%*	*No.*	*%*	*(mo)*	*rations*	*Home*
Injury	1,130	588	52	542	48	22	75	75
Death	41*	25	61	15	37	15	100	97

*One child was not identified by sex.

product or products involved, and location of the accident. The reporting of the information permits an accrual of data that are analyzed on a monthly and yearly basis. Foods and food parts, including nuts, bones, etc, are not recorded in this data base.

Our analysis included all reported emergency room encounters for FB/AI for ages 0 to 3 years for the 2-year period 1988 and 1989. However, product-related deaths for a 3-year period (1988 through 1990) from FB/AI were analyzed to obtain larger numbers. All the information obtained is part of the public record of the CPSC and was obtained from its computer printouts.

RESULTS

Product Morbidity Data. The 2 years of injury analysis (1988 and 1989) included 1,130 emergency room visits for FB/AI injury. The average age for children injured was 22.75 months. Slightly over one half (52%) of the children were young boys (see Table).

At least three quarters of all injuries were reported to occur in the home. The sites of the remaining one quarter were unspecified. All the children brought to the emergency room were evaluated, and 93% were released without overnight hospitalization.

Analysis of the type of choking event that occurred reveals that more than 95% of foreign bodies are designated "ingested" and less than 5% as "aspirated" by the emergency room staff. Of the 7% of children who were admitted for hospitalization, 12% had "aspirations."

Careful study of the offending objects reveals the following trends (see Figure, A). Coins were involved in over 50% of all emergency room encounters. (The range over the 2 years was from 51% to 53.8%.) The frequency was pennies 63%, nickels 10%, quarters 6%, and dimes 5%. Unspecified coins made up 15% of the total. This distribution mimics that of coins in circulation: pennies 74%, nickels 7%, dimes 10%, and quarters 9% (personal communication, US Mint Public Information Bureau, Washington, DC).

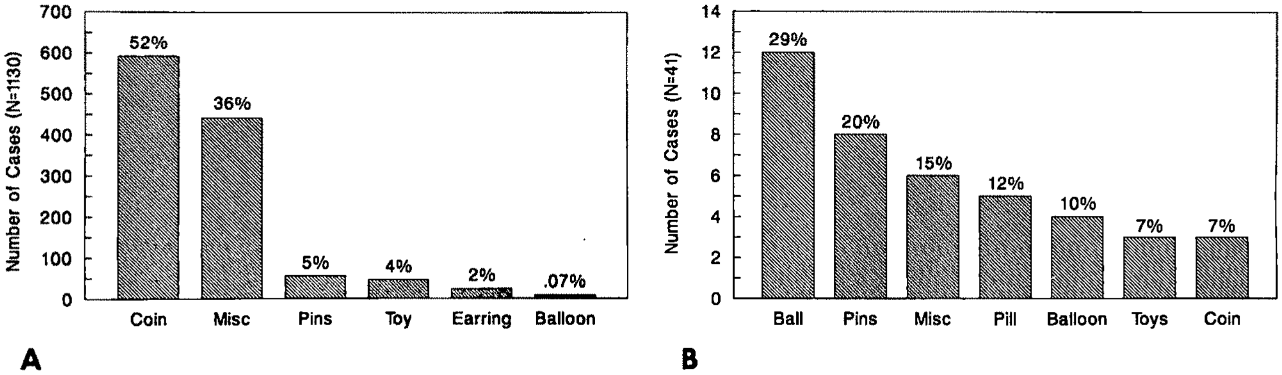
The remaining objects were various in frequency, size, and shape. Present in much smaller groupings (each less than 6%) were several common objects. Slender shapes, such as pins, needles, and screws, were second to coins at approximately 5%. Toys were in third place at just under 4% of choked-on objects. Jewelry, including earrings, accounted for approximately 2% of the total. Balloons, although often implicated in fatalities, were detected in only 0.7% of children (see Figure, A).

Product Mortality Data. Three years of NEISS data (1988 through 1990) were reviewed. A total of 41 deaths from product FB/AI occurred at the reporting hospitals. The average age at death was 14.8 months. More than half were boys (61%). Virtually all deaths (97%) occurred at home. The racial distribution was similar for the mortality and morbidity groups.

The offending objects associated with a fatal outcome included spheres in almost one third (30%; see Figure, B). The second most common fatal grouping was pointed objects (needles and screws) in approximately 20%. Medications, such as pills, were less common (12%), followed by balloons (10%). Toys were reported in three deaths (7%) in 3 years, and included toy parts.

DISCUSSION

This study of the data obtained through NEISS



Graphic presentation of data from National Electronic Injury Surveillance System. Children are 0 to 3 years old. Foods are excluded. A) Children's injuries by aspiration or ingestion, 1988-1989. B) Children's deaths from aspiration, 1988-1990.

continues to demonstrate a high propensity for young children to explore their environment and risk injury. Accidental FB/AI remains a health problem. Fortunately, 9 of 10 "choking" events, although alarming enough to prompt an emergency room visit, have a benign outcome. Over 93% of children are released to home.

For the remaining 7%, the injury was serious and required hospitalization and/or transfer to another hospital facility. There were no in-hospital deaths reported. The hospital mortality rate for FB/AI has been remarkably reduced, from over 50% to about 0% in the last 70 years.

The strikingly high incidence of coin ingestions remains noteworthy. The most common were pennies, which are 10 times more frequent in FB/AI than dimes or quarters, and 6 times more common than nickels. The survivorship for coin FB/AI (ie, passage through the gastrointestinal tract or endoscopic removal) has become better for all children who reach an appropriate health care facility, through appropriate diagnostic radiographs and/or endoscopic removal. The three deaths from coins occurred at home, prior to hospital evaluation.

There are two noteworthy differences between the morbidity and mortality data. The age in months for risk of death is significantly younger (13.4 versus 22.7 months). Also, there is a significantly higher male preponderance in the death category compared to the morbidity category (61% versus 51%). Overall, male children appear much more at risk for a fatal outcome, and more prone than girls to be involved in an injury from consumer products.

Also, "aspiration" was recorded to have occurred at about 5% of the total number of events, and is 2½ times more likely than "ingestion" to result in hospitalization. However, critical diagnostic evaluations to confirm aspiration, such as radiographic fluoroscopy and bronchoscopy, are not regularly used in the emergency room. Clinical judgment alone may predispose such children to have the seriousness of the aspiration missed or diagnosed late.

Bronchoesophagologists who work in tertiary care hospitals evaluate those children who require hospitalization for FB/AI. Our data show that it is 19 times more common for children following FB/AI to be discharged from the hospital emergency room than to be hospitalized. Retrospective studies of hospitalized children may miss some types of products causing substantial injury.

Several important factors of FB/AI analysis are missing from this data base. Foods and food parts are well recognized as the most common causes of choking events, but are not reported in this analysis. Also, our sampling of hospitals is widely distributed, but is based on patient referral patterns and population demographics developed almost 20 years ago when NEISS was initiated. Recently, more tertiary care centers, such as university or children's hospitals, care for the child with FB/AI. Do the present data compare with the FB/AIs treated at tertiary care centers? Direct referrals from emergency physicians to tertiary care institutions are also not included in this analysis.

Accurate detail on the exact size and shape of aspirated foreign objects is not available. Specific, accurate data would be useful to better understand and analyze the mechanics of FB/AI. The mortality and morbidity data from NEISS should address shape and size of those foreign bodies that lodge and persist, causing injury. Future studies should be directed toward a comparison of our data to similar data from children's hospitals.

CONCLUSIONS

Coins remain the most common foreign objects (52%) that are aspirated or ingested in children 0 to 3 years old. Boys have more injuries and risk of death. Over three fourths of injuries and more than 90% of deaths occur in the home. Spherical objects (eg, balls and pills) are most likely to cause asphyxiation (41%). Therefore, the highest risk is for the 2-year-old male child in the home. The parents, the home environment, and product design should be addressed for prevention and improved child health. Further analysis of shape and size of foreign bodies is indicated.

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Ann Otol Rhinol Laryngol 101:1992

PEDIATRIC AIRWAY MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX

DEBORAH MITCHELL BURTON, MD
SAN ANTONIO, TEXAS

SETH M. PRANSKY, MD
SAN DIEGO, CALIFORNIA

RICHARD M. KATZ, MD
SAN DIEGO, CALIFORNIA

DONALD B. KEARNS, MD
SAN DIEGO, CALIFORNIA

ALLAN B. SEID, MD
SAN DIEGO, CALIFORNIA

Gastroesophageal reflux (GER) in children may be classified as physiologic or pathologic, depending on its degree and consequences. There are many head and neck complications of GER in pediatric patients, but most numerous are the airway manifestations, including stridor, recurrent croup, exacerbation of subglottic stenosis, laryngeal irritation with or without laryngospasm, chronic cough, and obstructive apnea. Diagnosis may be difficult unless there is a high index of suspicion for GER and awareness of the concept of "silent" GER. We present the common pediatric airway manifestations of GER, illustrated by case reports, and provide a paradigm to assist in the diagnosis and management of children with airway compromise associated with GER.

KEY WORDS — apnea, gastroesophageal reflux, pediatric airway compromise, silent gastroesophageal reflux, stridor, subglottic stenosis.

INTRODUCTION

Gastroesophageal reflux (GER) describes the retrograde movement of gastric contents into the esophagus. The refluxed material, which may contain acid, pepsin, bile acids, and pancreatic enzymes, has the ability to irritate or injure tissues not adapted to the presence of these potentially noxious materials.[1,2] Gastroesophageal reflux is common in infants and children and can result in serious morbidity and even mortality. The natural history of GER without active therapy was documented in 1959.[3] The need to identify and treat this entity can thus be appreciated.

The classic symptoms of pediatric GER-induced tissue injury are emesis, dysphagia, rumination, burping, choking, gagging, and failure to thrive. Heartburn is not a prominent symptom in children.[4] Recently, attention has been focused on the head and neck manifestations of GER.[4-7] A multitude of pediatric airway complications has been associated with GER, frequently in children who do not demonstrate the classic symptoms of GER. A high index of suspicion is required to accurately diagnose and treat airway disease in these patients.

CLASSIFICATION

There are various classifications of GER. The most basic approach is to separate GER into physiologic and pathologic forms. Episodic reflux may be a physiologic phenomenon, particularly in the postprandial period. Children with physiologic reflux have infrequent episodes of emesis. Pathologic GER occurs when the frequency of refluxing becomes greater than that in the physiologic state, leading to symptoms or disease. The clinical delineation of pathologic from physiologic GER may be extremely difficult.[8] The esophageal pH has been studied in infants of various ages. The total percentage of time that the pH was less than 4 averaged 7%, with a range of 3% to 11%.[9] Thus, reflux greater than 7% is an accepted standard differentiating physiologic from pathologic GER. Because infants from 3 to 9 months of age may spend an average of 9% to 10% of the time with a pH less than 4,[9] some institutions may opt to use this higher upper limit to define pathologic GER.

Children with pathologic GER may have frequent, daily episodes of emesis; however, the concept of "silent" GER must be understood and appreciated in this group of patients. Kennedy[10] described silent GER in association with respiratory problems in 1962 and was one of the first authors to document that significant GER may occur in the absence of classic symptoms. Pathologic GER may lead to a variety of

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From the Departments of Pediatric Otolaryngology (Burton, Pransky, Kearns, Seid) and Pediatric Gastroenterology (Katz), Children's Hospital and Health Center, San Diego, California. Dr Burton is currently at Brooke Army Medical Center in San Antonio, Texas. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or Department of Defense.

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REPRINTS — Seth M. Pransky, MD, 3030 Children's Way, No. 402, San Diego, CA 92123.

disease processes due to esophageal involvement (esophagitis, stricture, Sandifer's syndrome) and may manifest as nutritional (failure to thrive, feeding difficulties) or behavioral problems (sleep disturbances, excessive crying).[5,6,8,11,12] Respiratory manifestations that should heighten suspicion for GER-associated diseases are stridor, recurrent croup, subglottic stenosis, laryngitis, laryngospasm, chronic cough, and obstructive apnea in the upper airway, and recurrent pneumonia, recurrent bronchitis, asthma or bronchospasm, and bronchopulmonary dysplasia in the lower airway. Physiologic GER may become pathologic GER at any time during its course, and the difference between them is not related to the frequency or duration of symptoms.[12]

DIAGNOSIS

An accurate diagnosis of GER starts with a high index of suspicion. A history is helpful in children who have the classic symptoms; however, in the absence of these symptoms, silent GER can only be ruled out by further studies. The evaluation for GER ideally should demonstrate the presence or absence of reflux, the severity of the reflux, and the identification of reflux as the cause of the child's symptoms.[13] There is no single test that can fulfill all of these criteria; thus, a combination of tests is often employed. The most commonly used tests are esophageal pH monitoring, the upper gastrointestinal (UGI) series, the nuclear medicine scintiscan, esophagoscopy with or without biopsy, bronchoscopy with lipid-laden macrophages (LLMs), and a modified Bernstein test.

The gold standard for diagnosis of GER is prolonged esophageal pH monitoring in conjunction with a history of subjective symptoms. This test documents multiple parameters, including the daily percentage of reflux and the duration of reflux episodes. Reflux of acidic material is readily determined, but an acid-neutral refluxate may not be identified. To enhance the efficacy of prolonged esophageal pH monitoring, we discontinue all histamine H2 receptor antagonists 72 hours prior to testing and have the parents log in a diary the patient's symptoms and food intake during the test period. Although certain dietary items may immediately interfere with precise readings, the prolonged nature of the study usually allows for an accurate diagnosis to be made. Significant GER may go undetected if the refluxate is alkaline, as in "bile" reflux. If this is suspected, we proceed with one of the other diagnostic tests that do not rely on acidification. We do not feel that esophageal pH monitoring for short intervals of time using provocative measures to induce GER, such as Valsalva maneuvers, are as reliable as an 18- to 24-hour monitoring period; thus, this method of evaluation is not recommended. Barium swallow studies are useful to visualize anatomy, but the sensitivity for reflux is low.

It is important to document the lack of a tracheoesophageal communication, gastric outlet obstruction, and partial malrotation, all of which may be surgically correctable and may exacerbate GER-associated airway symptoms. Nuclear medicine scintiscans can detect delayed gastric emptying, as well as pulmonary aspiration of gastric material. Esophagoscopy does not detect GER itself, but does evaluate esophageal mucosal abnormalities; however, normal mucosa does not rule out GER. Biopsies may increase the diagnostic yield, but significant GER may occur in the absence of esophagitis. Esophagitis may also be evaluated via suction biopsies of the esophageal mucosa.[14,15] Direct visualization is not achieved, but this technique may yield additional information without the need for sedation.

Bronchoscopy to identify laryngotracheal mucosal abnormalities, with tracheal aspirates for LLMs, has achieved an increasingly popular role in the diagnosis of GER with aspiration. Wynne et al[16] demonstrated in mice that microaspiration of gastric contents in quantities insufficient to lead to aspiration pneumonia could cause significant tracheal mucosal damage. Aspiration of gastric contents was most damaging when the pH was low. Evaluation of tracheal aspirates for LLMs has been studied extensively.[17-19] The conclusion has been that the presence of LLMs does not solely indicate gastric content aspiration, since a variety of irritative phenomena may induce LLMs; however, patients with gastric content aspiration may have a greater quantity of LLMs per high-power field. As the sensitivity of LLMs in detecting GER with aspiration is 85%, the absence of LLMs does not rule out GER.[19] Further evaluation should be pursued if clinical suspicion is high. Because of the high rate of respiratory symptoms associated with GER, it has been recommended that bronchoscopy be routinely carried out at the time esophagoscopy is performed.[20] Bronchoscopy will alleviate concerns of an associated primary anatomic or physiologic airway abnormality, as well as determine the extent of laryngotracheal mucosal damage secondary to GER. A variety of airway findings can be seen with GER, as will be discussed later in this paper.

The Bernstein test was originally designed to diagnose esophagitis via reproduction of the patient's symptoms by acid directly perfused onto the distal esophagus. A modified Bernstein test may be useful in determining GER as the cause of bronchospasm or stridor when the acidification of the distal esophagus induces these symptoms. The mere presence of GER and these airway symptoms does not indicate that the two are related.[14,21,22] Although this test is the definitive one to prove a causal relationship, we feel it is seldom required. A trial of medical management for documented GER and monitoring of the airway symptoms is warranted. In the event of persistent airway symptoms with persistent GER, surgical management is justified. The modified Bernstein test may be best used when standard evaluations for GER have been negative but a high index of suspicion is still present. Acidification of the distal esophagus that reproduces the airway symptoms in these patients may then justify the treatment of previously undocumented GER. From a practical standpoint, if GER is documented in association with respiratory compromise, we do not feel the modified Bernstein test adds any information that would alter our management plans.

TREATMENT

Treatment of GER depends on the severity of the child's symptoms and their response to conservative management. In general, the vast majority of patients are successfully treated with a combination of conservative or traditional (dietary, positioning, behavioral) and pharmacologic therapies. Pharmacologic agents (antacids, prokinetic agents, H2 blockers) are not usually employed until pathologic reflux is documented. Prokinetic agents such as metoclopramide are useful for acid and alkaline reflux, because these agents increase the gastric emptying rate as well as the tone of the lower esophageal sphincter. Bethanechol chloride, which was once thought to be a prokinetic agent, has been recently shown to improve GER by enhancing esophageal acid clearance via enhancement of saliva production.[23,24] The H2 blockers such as cimetidine and ranitidine hydrochloride are often used later in medical management when persistent acid reflux occurs. Neutralizing the refluxate to a more alkaline pH has been shown to lessen the damage to the upper airway mucosa.[6,7,16] Surgical intervention (fundoplication, gastropexy) should be reserved for medical management failures. In instances of life-threatening airway events or in critically ill children, surgical management may be a first line of therapy.[8,11]

Decision-making in the evaluation and treatment of GER may be difficult. Most patients do not require all tests or all treatment modalities. When airway symptoms are present, GER is considered moderate to severe.[11] Several case reports are provided to demonstrate important features of the history, workup, and treatment of GER-induced pediatric airway disease.

CASE REPORTS

CASE 1

A 16-month-old boy, the product of a full-term (FT) normal spontaneous vaginal delivery (NSVD), was intubated for 2 weeks during treatment for Guillain-Barré syndrome. Several days after extubation, the child developed stridor that failed to improve with medical management. He underwent laser therapy for subglottic granulation tissue, but this only transiently improved his airway. On referral to our facility, a bronchoscopy was performed that demonstrated a 60% circumferential subglottic stenosis (SGS). A one-stage laryngotracheoplasty was performed in lieu of a tracheotomy.[25] The airway symptoms resolved for 3 weeks. Repeat bronchoscopy revealed recurrent SGS with abundant granulation tissue that was unresponsive to laser therapy. Although the child had no symptoms to suggest GER, findings of a screening UGI series were normal. An esophageal pH probe was placed and documented multiple prolonged episodes of GER. Medical management for GER was instituted. Bronchoscopy 1 month later revealed a mild (15%) SGS without granulation tissue. He had no further airway compromise.

Comment. Intubated patients are at risk for increased subglottic injury secondary to GER. Increased SGS has been documented in animal models when gastric secretions were applied to traumatized subglottic lumens.[6,7] Attempts to correct the SGS will be unsuccessful until the GER is treated. In 1983, Bain et al[5] described the first reported case of SGS refractory to surgical management until GER was treated. Further support for treatment of GER to enhance successful laryngotracheal reconstruction of SGS was documented in 1987.[26] The case we described was our index case that demonstrated the significant role GER played in airway problems unresponsive to standard therapy. We agree with others[5,7,26] in recommending routine evaluation to exclude GER in patients with SGS prior to proceeding with surgical correction. An aspirate for LLMs was not taken in this patient and may have been helpful in making the diagnosis of GER earlier. The failure of the UGI series to demonstrate GER in this patient confirms reports of low sensitivity of UGI series to detect GER. If GER is suspected, prolonged esophageal pH monitoring or a scintiscan should be performed.

CASE 2

A 2-month-old boy, the product of an FT NSVD, was noted to have intermittent stridor several weeks after birth. His stridor continued to worsen until it became continuous and caused feeding difficulties. There was no prior history of vomiting, but the child did occasionally choke while feeding. A UGI series and a lateral neck radiograph showed normal findings. Bronchoscopy demonstrated moderate laryngomalacia and posterior laryngeal erythema with a normal subglottis and trachea. Rare LLMs were found on a tracheal aspirate. The patient's stridor continued to worsen postoperatively. An esophageal pH probe was placed and demonstrated significant GER. His reflux was treated medically, and several days later the stridor was markedly improved. He remained with mild stridor more appropriate for his degree of laryngomalacia.

Comment. The differential diagnosis of stridor in infants is extensive, with laryngomalacia being the most common cause. However, when the airway distress is out of proportion to the degree of laryngomalacia present, a second explanation should be sought. A UGI series was performed to rule out an anatomic problem, but no GER was noted. Because of the laryngeal findings and our suspicions, further evaluation for GER was pursued with an esophageal pH probe. There has been thought to be an association between laryngomalacia and GER owing to a focal neuromuscular immaturity.[27] The prompt improvement in this patient's symptoms after GER therapy illustrates how the majority of children are amenable to medical management alone. Indeed, in cases of severe laryngomalacia that require surgical intervention, such as laser division of the aryepiglottic folds or epiglottoplasty[28,29] (also Pransky et al, unpublished observations, 1986), we have identified a clear association with GER. In these cases, we recommend a full evaluation and medical management of GER prior to surgical intervention for the laryngomalacia.

The cause of the GER-associated stridor is unclear. Nielson et al[30] reported seven infants with continuous stridor in association with GER. Polysomnographic data demonstrated increased airway obstruction with increased stridor and retractions in all infants during periods of reflux. That none of these patients had underlying laryngeal disease accounts for their total resolution of stridor after treatment of GER. Others[31] have found that the presence of anatomic or functional laryngeal disease increases the risk for stridor in patients with GER. Two causes have been suggested. One is that the superimposition of laryngospasm on an abnormal larynx increases the chances for stridor. The other is that the esophagitis associated with GER may produce marked irritability resulting in more rapid or forceful breathing, thus producing a relative airway narrowing on an already compromised larynx.[31]

CASE 3

An 11-month-old boy, the product of an FT NSVD who had a markedly positive family history for asthma and atopic diseases, presented with recurrent croup. He had three major episodes of croup within the first 9 months of life, with a tendency for "croupiness" between attacks. His baseline noisy breathing and cough slightly improved with antihistamine therapy; however, a bronchoscopy was performed because of the persistent airway symptoms. Posterior laryngeal edema and erythema was noted in conjunction with lateral subglottic wall inflammation. A tracheal aspirate for LLMs was negative. Two more episodes of significant croup occurred within the following 3 months. An esophageal pH probe was placed and documented active reflux for 17% of the 24-hour test time. Medical management was instituted. The patient had no further episodes of acute croup in the next 6 months, but continued to have some baseline noisy breathing due to his underlying reactive airway disease.

Comment. Cases 2 and 3 demonstrate how GER may exacerbate airway disease that can result in residual symptoms even after adequate treatment of GER. The early diagnosis and effective treatment of GER as an exacerbator of underlying disease may prevent unnecessary aggressive treatment for mild respiratory diseases. Case 3 also demonstrates how tracheal aspirates for LLMs may be misleading. The negative aspirate may have caused a delay in proceeding with a workup for GER. This case emphasizes the point that no single test will accurately determine the presence or absence of GER. A high index of suspicion should be the driving force to proceed with further testing.

CASE 4

A 1-day-old girl was the firstborn of a 33-week twin gestation. She was noted to have a nasopharyngeal mass antenatally. At the time of birth, no respiratory distress was apparent; however, several episodes of bradycardia ultimately led to elective intubation within the first hour of life. Magnetic resonance imaging and a computed tomography scan were performed to determine that the nasopharyngeal mass did not involve the cranial cavity. The mass was excised via a transoral approach, leaving a complete cleft of the secondary palate. The mass was found to be a nasopharyngeal hairy polyp. Postoperatively, feeding was delayed because of a weak gag reflex. One month later, the child returned for a routine follow-up examination. A history of poor feeding and

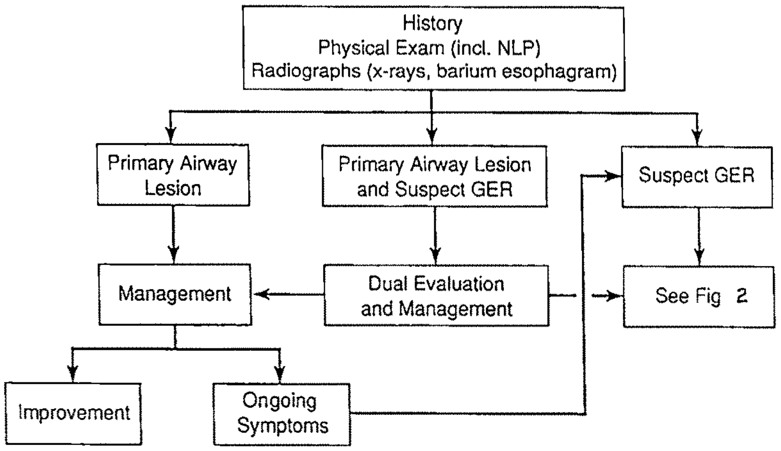
History
Physical Exam (incl. NLP)
Radiographs (x-rays, barium esophagram)
Primary Airway Lesion
Primary Airway Lesion and Suspect GER
Suspect GER
Management
Dual Evaluation and Management
See Fig 2
Improvement
Ongoing Symptoms

Fig 1. Paradigm for management of pediatric airway compromise. NLP — nasopharyngolaryngoscopy, GER — gastroesophageal reflux.

noisy breathing was obtained. While in the office, the child suffered a severe apneic episode with cyanosis and was emergently admitted to the hospital. A UGI series was performed and demonstrated a sliding hiatal hernia and severe GER with distal erosive esophagitis. The patient was having continual episodes of apnea and bradycardia that were life-threatening. Medical management, including a prokinetic agent and an H_2 blocker, was attempted for 3 days. The severe episodes of apnea that intermittently required resuscitative measures continued. Because of the life-threatening nature of the patient's problems, a fundoplication was performed. Within 48 hours, the episodes of apnea resolved. Mild intermittent bradycardia continued for 2 weeks. The child continues to do well, tolerating oral feedings without respiratory compromise.

Comment. This case graphically illustrates how a standard trial of medical management for GER may be bypassed in the event of life-threatening airway compromise. Although the airway was secured by the fundoplication, not all the damage from the GER had healed. It is important to bear in mind the nonrespiratory manifestations of GER before determining that medical therapy may be stopped. This patient remained on some medical therapy as treatment of her severe esophagitis for several weeks, and follow-up will be needed with the gastroenterologists to ensure that an esophageal stricture does not develop.

DISCUSSION

Gastroesophageal reflux is often a benign, self-limited problem of infancy and early childhood, usually manifested by frequent episodes of emesis. Symptoms related to airway compromise have been widely recognized in association with GER. A history suggestive of GER may not be present in these patients, as their airway compromise can be the only symptom of silent GER.

There are many mechanisms for GER-associated airway disease. Direct acid-induced mucosal damage of the upper airway is of primary concern for the otolaryngologist. However, reflex-mediated mechanisms are also extremely important and may lead to laryngospasm, bronchospasm, and apnea without direct involvement of acid on the upper airway mucosa.[14,15,21,22] Conversely, it has been recognized that primary airway disease and its treatment may induce GER.[15] Respiratory disorders or symptoms may provoke GER if they alter any of the antireflux barriers. Some of the more common examples include positive abdominal pressure increases associated with coughing and wheezing, negative intrathoracic pressure increases associated with stridor and hiccups, cigarette smoking or medications such as theophylline that relax the lower esophageal sphincter, and chest physiotherapy that induces GER through provocative positioning and possibly forced expirations and cough manuevers.[15] Thus, with the coexistence of GER and airway disease, careful assessment is warranted to determine which disease process is primary and which is secondary. This differentiation is important for accurate treatment of the patient's problem.

Absolutes in diagnosing GER and in turn identifying reflux as the cause of the patient's symptoms do not exist; however, prolonged esophageal pH monitoring is accepted as the gold standard. Because this test does not diagnose persistent GER if the refluxed material is alkaline, follow-up by this method may be difficult if H_2 blockers have been used and persistent symptoms exist. Although the injury they cause is less severe, gastric contents with a higher pH may still cause significant airway damage.[6,7,16] Further evaluations may need to rely on barium swallow studies, scintiscans, and endoscopy.

The key to accurately treating and following up patients with airway compromise associated with GER is to think of the diagnosis. Physicians often do

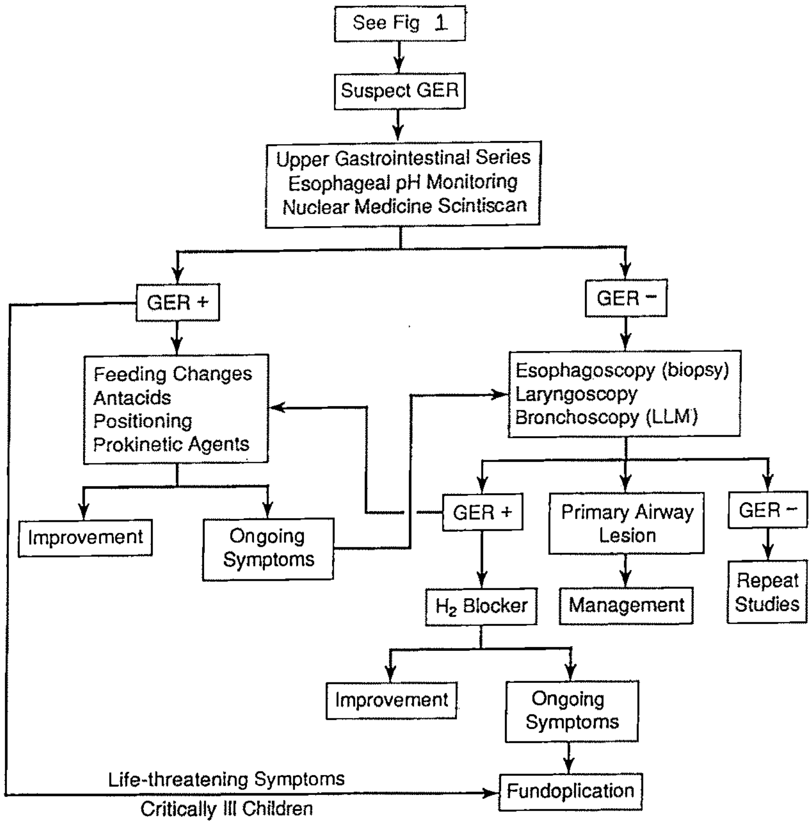

Fig 2. Paradigm for management of pediatric airway compromise with raised index of suspicion for gastroesophageal reflux. LLM — lipid-laden macrophages.

not consider the potential connection between refractory airway symptoms and GER while evaluating patients. The concept of silent GER is critical in understanding the inclusion of GER in the differential diagnosis of airway compromise in children who infrequently regurgitate.

We present our paradigm for the management of pediatric patients with airway compromise and illustrate how a raised index of suspicion for GER should influence treatment plans (Figs 1 and 2).

A screening airway evaluation in our patients involves a thorough history and physical examination that includes flexible nasopharyngolaryngoscopy. Flexible nasopharyngolaryngoscopy is critical for functional evaluation of the larynx for diagnoses such as vocal cord paralysis and laryngomalacia. The glottic and supraglottic anatomy is also well assessed with nasopharyngoscopy. A high-voltage neck x-ray study, which enhances airway visualization with decreased soft tissue detail, may demonstrate SGS, cysts, or tumors. Barium esophagrams or magnetic resonance imaging may be indicated if a vascular abnormality is suspected. After the initial evaluation, a tentative diagnosis may be made. If a primary airway lesion is suspected, appropriate management should be instituted. This may include further diagnostic tests, radiographs, medications, endoscopy, or open surgical procedures. After treatment, the patient is reassessed. If the symptoms have not improved as anticipated, an underlying diagnosis of GER should be ruled out. Some patients will have a primary airway lesion in addition to GER. When this is suspected, a dual evaluation and treatment plan for both problems is warranted. In the event that the initial airway screen does not reveal evidence for a primary airway lesion, the suspicion for GER should be high and an evaluation should be initiated.

We perform our GER evaluation in concert with the pediatric gastroenterology service. A UGI series is a frequent screening test. Although this test has a low sensitivity for GER, it is useful in documenting normal anatomy. A partial gastric outlet obstruction or malrotation may cause GER that is refractory to standard therapy. Ultimately, any patient referred for fundoplication must have a UGI series to demonstrate normal anatomy. When airway compromise requires more urgent care, the evaluation may begin directly with esophageal pH monitoring or a scintiscan. Our collective experiences in a number of different institutions have shown that the decision to perform esophageal pH monitoring rather than a nuclear scintiscan depends on the availability of the studies and the clinician's expertise in performing and interpreting them. Nuclear scintiscans are less reliable in the diagnosis of GER at our institution; thus, we perform esophageal pH monitoring regularly. Other institutions with proven track records for accurate diagnosis of GER with scintiscans may use this modality initially and reserve esophageal pH monitoring for the more refractory cases. Consultation with the gastroenterologists at individual institutions should allow for clarification of which modality is reliable for the diagnosis of GER in their pediatric patients.

After GER is diagnosed, a trial of conservative management along with a prokinetic agent, such as metoclopramide, is recommended; however, life-threatening symptoms may be an indication for urgent fundoplication. Reassessment of the patient is performed 6 to 8 weeks after therapy. If ongoing symptoms are present, an endoscopic evaluation is performed. Endoscopy is also indicated when there is a high index of suspicion for GER but the initial GER screening evaluation is negative.

Esophageal evaluations are performed in our institution via esophagoscopy with or without biopsy. Evidence of severe esophagitis, such as ulcerations or mucosal slough, precludes the need for tissue biopsy. While some institutions employ blind suction esophageal biopsies, we feel that children with suspected airway compromise related to GER are best treated with direct visualization of the esophagus and upper airway.

Common laryngeal mucosal abnormalities that we have found in association with GER include posterior laryngitis, hypertrophic interarytenoid tissue, edematous vocal cords, diffuse supraglottic edema, vocal cord granulomas, and subglottic inflammation. In the tracheobronchial tree, GER-induced mucosal abnormalities may occur as "cobblestoneing" along the posterior tracheal wall, diffuse mucosal edema, blunting of the carina, and friable mucosa. An unsuspected primary airway lesion may also be found during endoscopy and should be managed appropriately. In the uncommon event that a complete evaluation reveals no evidence of a primary airway lesion or GER, it is recommended that the patient be monitored closely and possibly undergo a repeat evaluation. We prefer not to treat patients in whom GER cannot be diagnosed by at least one method, because an end point to therapy is unclear. Furthermore, patients with persistent symptoms in the face of maximal therapy cannot be referred for fundoplication if GER has not been demonstrated. Since GER can be intermittent, we recommend repeating negative studies if the suspicion for GER remains high. In these patients, the modified Bernstein test may also be applicable to demonstrate that esophageal acidification undocumented by previous studies can induce the patient's airway symptoms. All patients with persistent airway compromise and documented GER who fail to improve with medical treatment should be considered for fundoplication. In general, a failure is not determined before 6 weeks of therapy, but this rule can be modified according to the degree of airway symptoms.

SUMMARY

Gastroesophageal reflux in the pediatric population has a variety of manifestations. Airway compromise may bring children with this disease to the attention of otolaryngologists. A high index of suspicion is required to accurately diagnose the disease and treat these patients. We have presented a paradigm to assist in the management of pediatric patients with airway compromise associated with GER.

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THE UCSF OTOLARYNGOLOGY UPDATE: 1992

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DISTRIBUTIONS OF EUSTACHIAN TUBE GOBLET CELLS AND GLANDS IN CHILDREN WITH AND WITHOUT OTITIS MEDIA

SHOJI MATSUNE, MD, DMSC
PITTSBURGH, PENNSYLVANIA

ISAMU SANDO, MD, DMSC
PITTSBURGH, PENNSYLVANIA

HARUO TAKAHASHI, MD
KYOTO, JAPAN

The distributions of the goblet cells and submucosal glands in eustachian tubes (ETs) from children with or without otitis media (OM) were studied. From 12 temporal bone–ET specimens obtained from children 1 to 7 years old at death, representative vertically cut histology sections were selected, stained with periodic acid–Schiff–Alcian blue and hematoxylin, and studied by light microscopy. In children without OM, the density of the goblet cells was significantly lower in the roof than in the floor of the ET and was highest in the midcartilaginous portion; glands were most richly distributed near the pharyngeal orifice, and became less densely distributed toward the tympanic portion. In children with OM, the density of the goblet cells was significantly higher both in the roof and floor portions, and the glands were more richly distributed than in the ETs of children without OM. The possibility that the observed increase in ET secretory components in children with OM impairs the passage of air through these tubes is discussed.

KEY WORDS — eustachian tube, glands, goblet cells, otitis media.

INTRODUCTION

The eustachian tube (ET) is an expanded portion of the upper respiratory tract.[1] Its epithelium, like the epithelium of the nasopharynx,[2,3] consists of ciliated cells, secretory (goblet) cells, nonciliated cells, and underlying basal cells resting on a thin basement membrane.

Hiraide and Inouye[3] and Hiraide[4] reported on the distribution of the ciliated and nonciliated cells lining the tubal epithelium of normal human eustachian tubes. When viewed by scanning electron microscopy, the epithelial cells on the floor and inferior parts of the lumen appear to be mostly of the ciliated type, and the number of ciliated cells decreases gradually as one moves toward the tubal roof. Bak-Pedersen and Tos[5,6] studied ET mucosa by the periodic acid–Schiff (PAS)–Alcian blue whole-mount method and noted that the density of goblet cells was lower in the tubal roof than in the floor. They also reported that in specimens from individuals with otitis media (OM) compared to those without OM there were more glands in the middle ear (ME) mucosa and the density of goblet cells was higher in the tubal mucosa, especially in the tubal roof.

All of these observations[3-6] indicate that the distributions of such epithelial components as ciliated cells, nonciliated cells, and goblet cells seem to vary depending on the area of the ET viewed and depending on what changes have resulted from inflammation in the ME. To our knowledge, however, no detailed report has been issued concerning the spatial distribution of submucosal glands around the ET and the relationship of this distribution to ME inflammation. Furthermore, these structures seem never to have been investigated systematically through the entire ET and its accessory structures as a whole. For these reasons, we undertook to study in detail the spatial distribution of secretory components (goblet cells and submucosal glands) surrounding the tubal lumen. We investigated this topic by examining serial histology sections of specimens that included the entire ET and its accessory structures and comparing these structures in specimens from children with and without OM.

MATERIALS AND METHODS

Twelve human temporal bone specimens with the entire ET and its accessory structures were used. Seven of them were from children with OM, 2 to 7 years of age (mean ± SD, 3.0 ± 2.2 years) at death; of those seven children, six had had chronic OM and one had had acute OM.[7] The remaining five specimens were from children 1 to 6 years of age (average age 3.8 ± 1.9 years) who did not have OM at the time of death and were used as controls. All of these specimens were removed and processed histologically according to the technique described by Sando et al.[8]

Serial 30-μm-thick histology sections were cut

From the Elizabeth McCullough Knowles Otopathology Laboratory, the Division of Otopathology, Department of Otolaryngology, University of Pittsburgh School of Medicine, Eye and Ear Institute of Pittsburgh, Pittsburgh, Pennsylvania. This study was supported by National Institutes of Health Research Grant DC 00158.

REPRINTS — Isamu Sando, MD, DMSc, Division of Otopathology, Eye and Ear Institute of Pittsburgh, 203 Lothrop St, Pittsburgh, PA 15213.

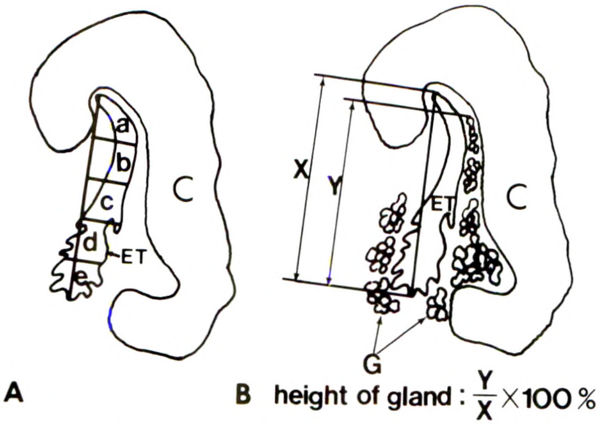

Fig 1. Outline drawings of cross section through midcartilaginous portion of eustachian tube (ET) and its surrounding structures. C — eustachian tube cartilage. A) Five areas (a, b, c, d, and e) of ET defined to analyze distribution of epithelial goblet cells. B) "Height of gland" used to indicate distribution of submucosal glands (G). X — height of ET, Y — height of gland.

vertically in the plane perpendicular to the long axis of the ET, from the pharyngeal orifice to the tympanic orifice. Every 20th section was stained with hematoxylin and eosin. First, the stained sections containing the promontory of the ME were studied to evaluate whether inflammation was present in the ME.[9] Then a representative histology section was selected from each of six vertical portions of the ET, numbered 1 to 6 from the pharyngeal orifice to the tympanic orifice: 1) pharyngeal orifice, 2) midportion between pharyngeal orifice and midcartilaginous portion, 3) midcartilaginous portion, 4) midportion between midcartilaginous portion and isthmus portion, 5) isthmus portion, and 6) midbony portion between isthmus portion and the most anterior margin of the tympanic ring. The nearest sections to the six sections from each ET were stained with PAS–Alcian blue and hematoxylin and were examined under the light microscope. For this study we looked especially at the distributions of goblet cells in the tubal epithelial lining and of submucosal glands around the ET.

To evaluate the distribution of goblet cells in the tubal epithelium, we calculated the density of these cells in each of five cross-sectional areas of the ET between the roof and the floor. The five areas from the roof to the floor of the ET (a to e) were defined as follows: a line representing the long axis of the tubal lumen in cross section was drawn between the most distant two points on the luminal margin, and this line was divided into five segments of equal length by drawing four lines perpendicular to the long axis of the tubal lumen (Fig 1A). Next, the density of goblet cells per 1 mm^2 for each of the five areas (a to e) was calculated from the total number of goblet cells in that area, the total length of the epithelial lining of that area (as measured with a Hitachi HDG-1111 digitizer tablet), and the thickness of the histology section (30 µm).

To evaluate the distribution of submucosal glands around the tubal lumen, we calculated the percentage of the distance between the upper margin of the gland

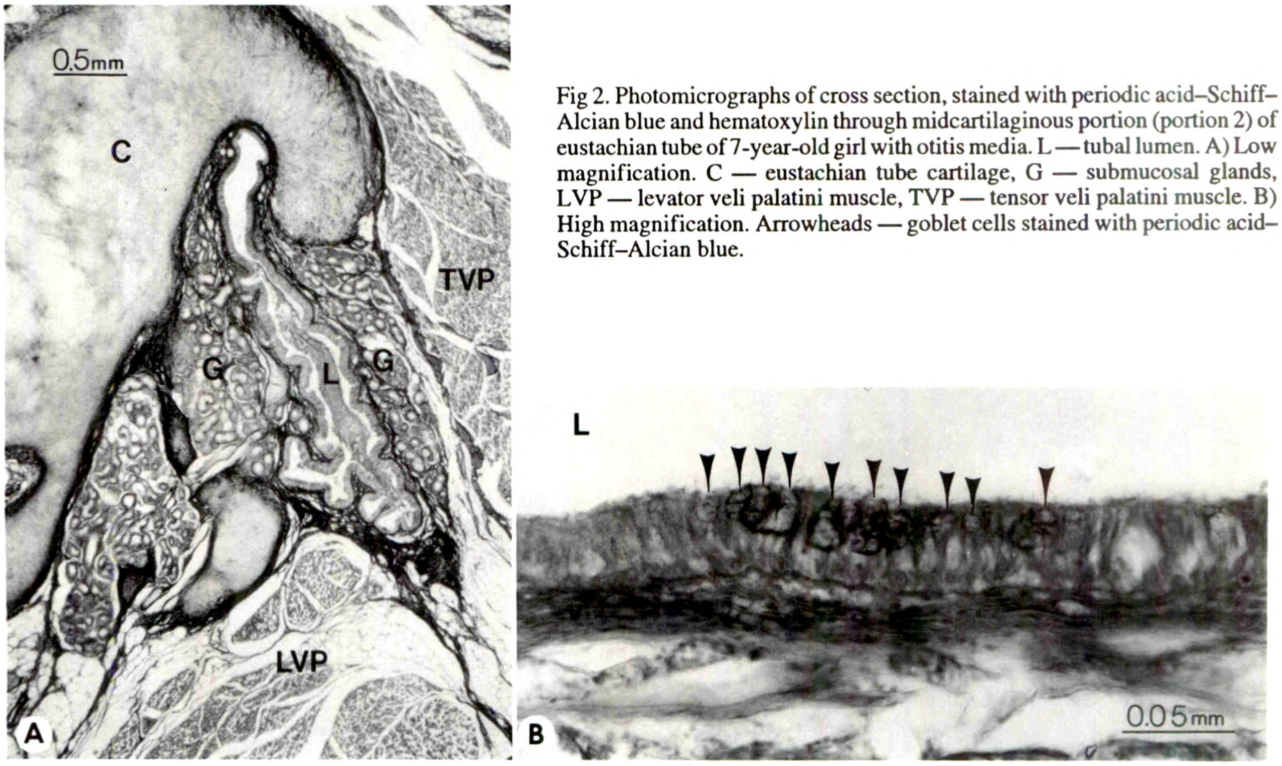

Fig 2. Photomicrographs of cross section, stained with periodic acid–Schiff–Alcian blue and hematoxylin through midcartilaginous portion (portion 2) of eustachian tube of 7-year-old girl with otitis media. L — tubal lumen. A) Low magnification. C — eustachian tube cartilage, G — submucosal glands, LVP — levator veli palatini muscle, TVP — tensor veli palatini muscle. B) High magnification. Arrowheads — goblet cells stained with periodic acid–Schiff–Alcian blue.

TABLE 1. EUSTACHIAN TUBE GOBLET CELL DENSITY PER SQUARE MILLIMETER

	Portion						
Area	*1*	*2*	*3*	*4*	*5*	*6*	*Average*
Control group (average of 5 cases)							
a	302.0	441.3	256.0	375.3	266.7	256.7	316.3
b	645.0	968.7	1,034.3	857.0	696.7	643.0	807.5
c	936.3	1,123.3	1,190.3	1,297.7	868.0	913.7	1,054.9
d	933.7	1,144.7	1,347.3	1,369.0	1,039.3	889.7	1,120.6
e	812.7	1,397.7	1,174.3	1,440.3	906.7	878.0	1,101.6
Average	725.9	1,015.1	1,000.4	1,067.9	755.5	716.2	
Otitis media group (average of 7 cases)							
a	504.7	464.3	571.3	631.3	515.7	827.3	585.8
b	767.3	1,023.3	1,005.3	1,279.3	1,242.3	1,361.3	1,113.1
c	758.0	1,101.3	1,524.3	1,298.3	1,273.0	1,672.3	1,271.2
d	842.7	1,343.3	1,351.0	1,462.0	1,564.7	2,068.0	1,438.6
e	735.7	1,195.0	1,662.7	1,453.7	1,588.3	3,065.3	1,616.8
Average	721.7	1,025.4	1,222.9	1,224.9	1,236.8	1,798.8	

See text for definitions of areas and portions.

and the tubal floor that contained glandular tissue. Thus, the length of the long axis of the tubal lumen in cross section was labeled X, the length of the tube surrounded by glands was labeled Y, and the "height" of the glands around the tube was Y/X x 100% (Fig 1B). We did not include glandular tissue located below the tubal lumen in this study because, whereas the upper margin of the gland in cross section is clearly defined, glandular tissue below the bottom of the tubal lumen usually extends to and merges with glandular tissue of the nasopharynx, making precise determination of the extent of ET glandular tissue in this area difficult.

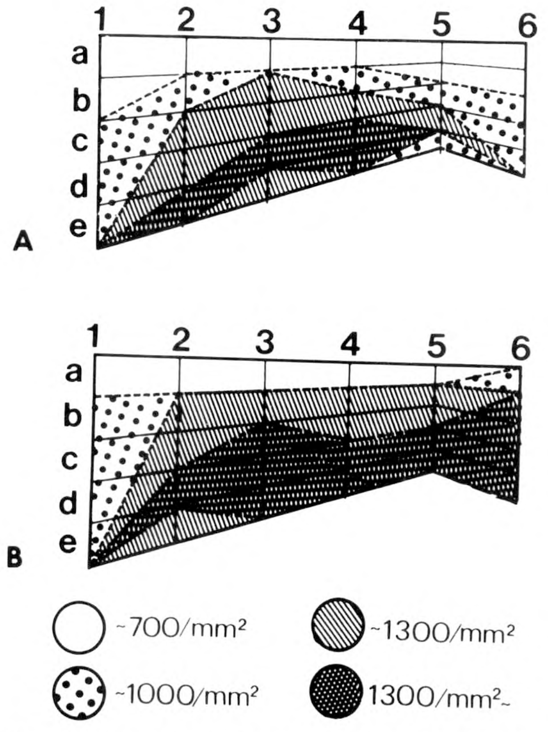

Fig 3. Graphic representation of densities of goblet cells in epithelium of eustachian tube both in cross section (areas a through e) and vertically (portions 1 through 6) in A) normal children (controls) and B) children with otitis media. See text for definitions of areas and portions.

RESULTS

Photomicrographs of a representative histology section from a 7-year-old girl with OM are shown in Fig 2: Fig 2A shows a low-magnification view of portion 2, and Fig 2B shows area d of that portion at higher magnification. In this case, the density of goblet cells in portion 2 was 2,393.6/mm^2, and the height of the glandular tissue was 100%.

Goblet Cells. The densities of goblet cells (mean values) in all five cross-sectional areas (a to e) for each of the six vertical portions (1 to 6) for the control group and the OM group are shown in Table 1 and Fig 3. Two characteristics of the distribution of the goblet cells in controls were noticeable. First, the density of these cells as seen in cross section was greater in the floor than in the roof of the ET. In particular, the density of goblet cells in area a was significantly lower than the average density of all the remaining areas (b, c, d, and e) in all six portions (paired Wilcoxon's ranking test, $p < .05$ for each portion). Second, the density of goblet cells was greatest around the midcartilaginous portion in longitudinal aspect.

In the OM group, in most of the areas (a to e) in portions 2 to 6, the density of goblet cells was higher than in controls (Table 1 and Fig 3). It was particularly remarkable in portions 5 and 6: there were significant differences in density between these two groups in area e in portion 5 (Wilcoxon's ranking test, $p < .01$) and in areas a, d, and e in portion 6 (Wilcoxon's ranking test, $p < .05$). For all six portions of the ET, the average density of goblet cells was higher in area a in the OM group than in controls (Table 1). However, even in those with OM the density of goblet

TABLE 2. EUSTACHIAN TUBE GLAND DISTRIBUTION EXPRESSED AS HEIGHT OF GLAND (PERCENT)

	Portion					
	1	*2*	*3*	*4*	*5*	*6*
Control group (average of 5 cases)	95.4	90.0	84.8	56.2	13.0	11.2
Otitis media group (average of 7 cases)	93.7	96.3	89.1	76.5	27.4	18.3

See text for definitions of gland height and of portions.

cells in area a was still significantly lower than the average density of all other areas (b, c, d and e) in portions 2 to 6 (paired Wilcoxon's ranking test: portion 2, $p < .05$; portion 3, $p < .01$; portion 4, $p < .01$; portion 5, $p < .01$; and portion 6, $p < .01$).

Distribution of Glands. The height of the glands in the control and OM groups in the six lengthwise portions of the ET is shown in Table 2 and Fig 4. It was found that in controls, the height of the gland, which was greatest at the pharyngeal orifice, decreased gradually toward the ME. There was remarkably less lumen surrounded by glands in the bony portion of the ET in both control and OM specimens; there was more glandular tissue in all portions except the pharyngeal portion in specimens from the OM group than in controls, and the difference was particularly significant for portion 2 (Wilcoxon, $p < .05$).

DISCUSSION

Other investigators studied goblet cells and glands of the human ET in mucosa removed from the ET and examined by a whole-mount method[5,6] or in segmented temporal bone specimens embedded in paraffin and examined by a grid-mount method.[10] Compared to these methods, the celloidin embedding method we use seems superior, because our method permits accurate anatomic orientation of the entire and intact ET with its mucosa and glands (Fig 2A). Furthermore, our method was found to permit staining with PAS–Alcian blue, which is specific for secretory components; such staining facilitates identification and evaluation of the ET tissues of interest.

According to Bak-Pedersen and Tos,[5,6] in normal adults the density of goblet cells is very high at the pharyngeal orifice (9,332.6/mm^2 on average) and decreases steadily but markedly toward the tympanic orifice, whereas in children (9 to 14 years old) and premature infants the density curves are rather flat; ie, younger individuals did not show the same differences in densities as did normal adults. In the present study, we also failed to see a significant decrease in density of goblet cells from the pharyngeal orifice toward the tympanic orifice in controls (children 1 to 7 years old), although we did see a change in density. The change was greatest in the midcartilaginous portion. The density of goblet cells at the pharyngeal orifice in normal children in our study (725.9/mm^2 on average) was between the densities for children (2,639.5/mm^2 on average) and premature infants (377.1/mm^2) in the study by Tos and Bak-Pedersen.[6] From the results of that study and our own, we speculate that the density of goblet cells at the pharyngeal orifice increases with increasing age to form the pattern, seen in adults,[5,6] of constant decrease from the pharyngeal portion to the tympanic portion of the ET.

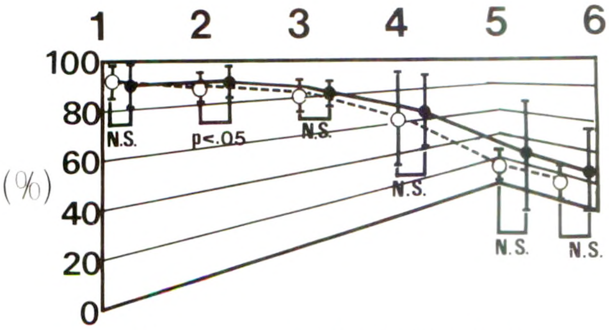

Fig 4. Graphic representation of distribution of submucosal glands as percentages of height of eustachian tube in six vertical portions (1 through 6) of eustachian tube in normal children (white circles with dotted line) and children with otitis media (black circles with solid line). N.S. — not significant.

A remarkable finding of the present study was that the highest density of goblet cells in the ETs of normal children is around the midcartilaginous portion (Table 1). Because the midcartilaginous portion of the ET, in which the tensor veli palatini muscle inserts into the lateral lamina of the tubal cartilage,[11] is considered to be the most dynamic portion of the ET, it seems reasonable that the density of goblet cells should be highest around this portion in normal children. A high density of goblet cells in this area would provide the surface of the tubal lumen with enough surfactant (surface tension–lowering substance)[12] to compensate for the poorer ability of the ET to open actively through early childhood (from 1 to 7 years of age) than in adulthood.[13]

In normal specimens in this study, in every portion of the ET from pharyngeal to tympanic, the density of goblet cells was significantly lower in the roof (area a) than in the floor (areas b, c, d, and e). Further, the submucosal glands did not reach the upper margin of the tubal lumen in normal specimens. From the present study of these two secretory components of the ET, then, the roof of the ET lumen seems to be less important in mucus production and secretion than the floor.

In comparison with controls in this study, specimens in the OM group had more goblet cells in the floor of the ET (areas b to e) in both the isthmus and midbony portions (portions 5 and 6, respectively). Considering that increased density of goblet cells is often seen with inflammation of the upper respiratory tract mucosa,[14] these findings in the isthmus and midbony portions seem to indicate more severe inflammatory conditions in these portions than in the cartilaginous portion. Such an analysis agrees well with the results of previous studies that showed that the bony portion of the ET tends to be easily involved secondarily by inflammation in the ME.[15,16] In addition, in these two portions the upper margin of the submucosal gland was markedly lower than in the cartilaginous portions, in both the OM group and the control group. The significantly greater density of goblet cells in these portions may result from compensation for the paucity of submucosal glands in this area: goblet cells may proliferate to serve the secretory function in ETs of individuals with OM because these individuals have inadequate numbers of submucosal glands.

In the OM group, remarkable increases in the goblet cells were seen in the roof area (area a) in all portions (1 to 6) of the ET (Table 1), but especially in the bony portion (portion 6; Fig 3B), although the density of cells in the roof of the ET was less than in the floor of the ET. The distribution of submucosal glands was also significantly richer near the pharyngeal orifice (portion 2) in those with OM versus controls (Fig 4). These findings suggest that an important function of the ET — serving as a passage for air — is preserved even in individuals with OM, although this function may be impaired by excessive secretion in this area.

In conclusion, our finding that in normal children 1 to 7 years of age the lining of the roof of the ET lumen is less richly supplied by secretory components than is the lining of the ET in individuals with OM supports the hypothesis of Sando et al[17] that the roof of the ET is important for the passage of air, and the floor for the passage of mucus. In individuals with OM, the function of this roof portion of the ET (ventilation of the ME) may be impaired to some extent by increased concentrations of secretory components, mainly goblet cells. These concentrations of secretory components aggravate tubal ventilatory dysfunction, particularly in the roof portion of the ET[16] in individuals with OM.

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Ann Otol Rhinol Laryngol 101:1992

FASCIA AND PERICHONDRIUM ATROPHY IN TYMPANOPLASTY AND RECURRENT MIDDLE EAR ATELECTASIS

RICHARD A. BUCKINGHAM, MD

CHICAGO, ILLINOIS

Fascia and perichondrium grafts to replace and reinforce thin, atrophic tympanic membranes (TMs) are recommended by several authors to correct middle ear atelectasis by forming a fibrous, collapse-resistant TM. This study reviewed the status of connective tissue grafts performed over the 10-year period from 1979 to 1988 to determine if these grafts would maintain sufficient strength and fibrous character to resist recurrent atelectasis. The author used fascia or perichondrium to repair 89 TM defects, and 63 ears were available for follow-up: 54 had cholesteatomas and 9 had perforations. Graft atrophy was judged by microscopic otoscopy and Kodachrome otophotography. Fascia TM grafts atrophied in 35 of 43 ears (80%), and perichondrium atrophied in 8 of 20 ears (40%). Grafts maintained their relatively thick and fibrous character in only 20 of 63 ears (32%). If fascia and perichondrium used to correct atelectasis were to atrophy at the same rate as the grafts in this series, atelectasis would recur after attempts to reinforce atrophic TMs. Atelectasis-prone middle ears require intubation despite surgery.

KEY WORDS — atelectasis, atrophy, fascia, graft, middle ear, perichondrium, tympanic membrane.

While following up on my own and other otologists' postoperative tympanoplasties, I have observed over several years a tendency of vein, fascia, and perichondrium grafts to atrophy, to become atelectatic, and even to develop retraction-type cholesteatomas.

Atelectasis is the result of chronic middle ear (ME) underaeration, and if fascia or perichondrium grafts are to correct or prevent ME collapse and maintain an air-filled ME, these grafts should maintain their fibrous character and strength over the years to resist chronic ME underpressure. Middle ear underaeration is a chronic condition that tends to persist and is not affected by ME surgery without intubation.

Along with other authors, I have favored intubation as a relatively simple, effective, and satisfactory treatment for moderate to severe degrees of ME atelectasis.[1-3] There are, however, other authors who have advocated, as a treatment for ME atelectasis, surgical replacement or reinforcement of thin, atrophic, collapsed tympanic membranes (TMs) with fascia or perichondrium.[4-8]

While many authors attribute ME atelectasis to defects in the eustachian tube, this appears to be an oversimplification. Middle ear aeration is now thought to be a complex process involving mucosal gas exchange, eustachian tube opening and closing, body position, movement of the TM, and status of the blood gases during waking and sleeping hours.[9,10]

I do not perform surgery for uncomplicated atelectasis, but prefer to treat this disorder by simple ME intubation. To quantify the incidence of TM graft atrophy, I reviewed 89 consecutive fascia and perichondrium grafts performed between 1979 and 1988 for chronic otitis media with perforations and for closed mastoidectomies for cholesteatomas. Twenty-six ears were lost to follow-up, leaving 63 for study. The status of the grafts was monitored by microscopic otoscopy and endoscopic photography.

Most of the cholesteatomas in this series were examples of far-advanced atelectasis with in-pocketing encystment into the ME or the lateral epitympanum. I make the assumption that the connective tissue grafts used to repair TM defects and cholesteatomas of this type will react biologically in the same manner as when they are used for atelectasis without cholesteatoma.

DATA ACCUMULATION

Records of surgery performed between 1979 and 1988 were reviewed. Only ears that were seen postoperatively for at least 1 year were included.

Most of the tympanoplasties, 54 of 63, were performed for relatively small early cholesteatomas limited to the ME and epitympanum. The bony external canal wall was preserved in all cases so that all operations were simple myringoplasties or canal wall up tympanoplasties of types I and III. The average age of all patients was 39 years (range, 7 to 74 years). There were 29 male and 34 female patients.

Temporalis fascia or tragal perichondrium was used in all cases and was positioned by the underlay technique. Ossicular transpositioning was used when

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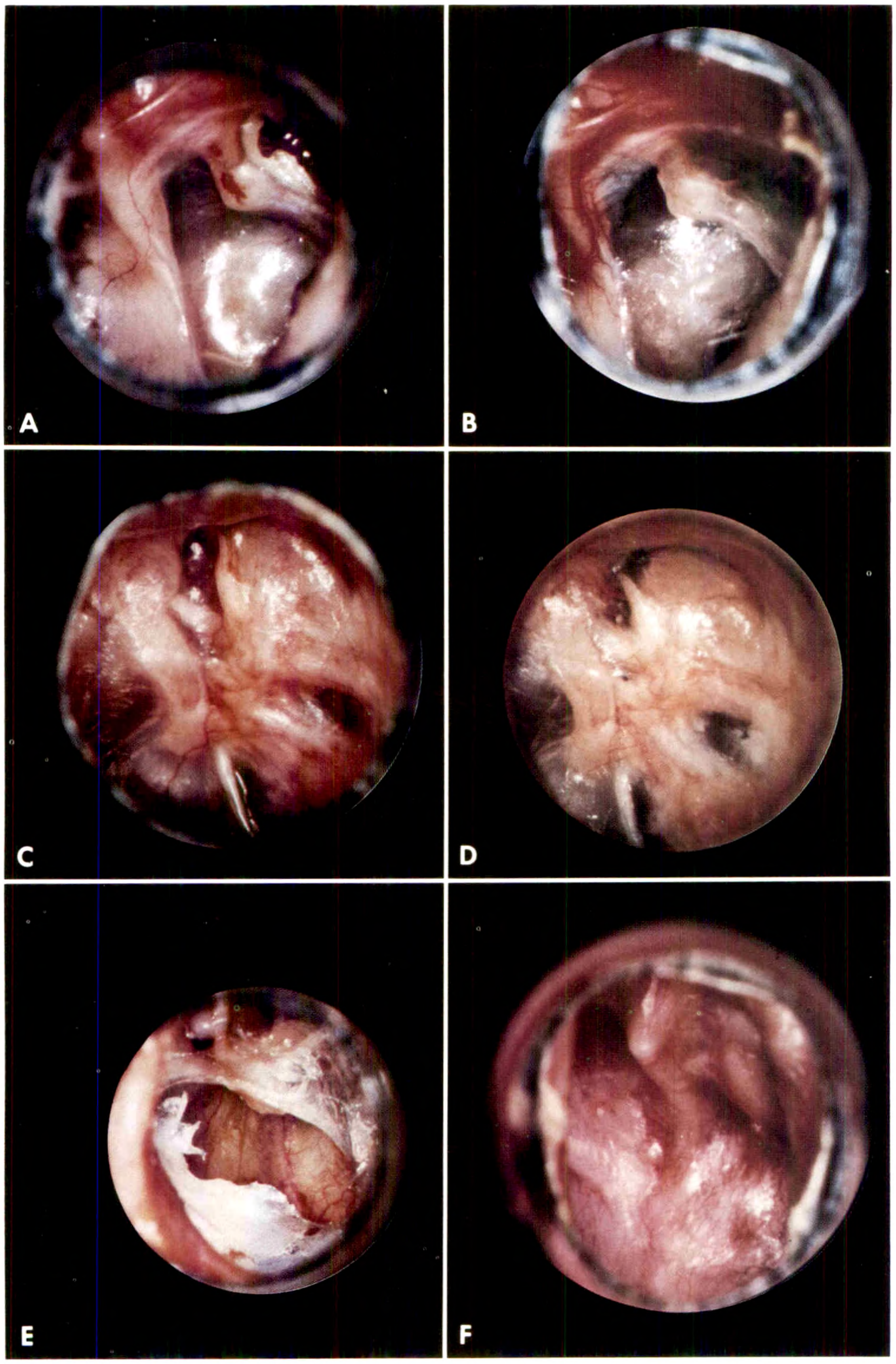
From the Department of Otolaryngology, University of Illinois College of Medicine, Chicago, Illinois.

REPRINTS — Richard A. Buckingham, MD, 145 S Northwest Highway, Park Ridge, IL 60068.



Results of tympanoplasty. A,B) (Case 1) A) Atrophic, atelectatic graft has collapsed into posterior half of middle ear onto promontory, and epithelial debris has accumulated in stapes crura, signaling tendency to cholesteatoma reformation. B) Eight months following repeat middle ear intubation, atelectasis has been corrected. Atrophic fascia graft has lateralized to level of stapes head and long process of incus. C,D) (Case 2) C) Intraoperative tube is extruded, and thin atrophic perichondrium has retracted into epitympanum in contact with transposed incus. D) Three months after intubation, atrophic graft has lateralized out of epitympanum while remaining in contact with transposed incus. E,F) (Case 3) E) Preoperative view of perforated TM following multiple intubations in childhood. There is stratified squamous epithelium on medial surface of anteroinferior TM segment. Perichondrium graft was inserted to close perforation after all TM cholesteatoma was removed. F) Two years later, atelectasis has recurred. Perichondrium graft has collapsed onto promontory and has partially enveloped malleus handle and long process of incus. This graft was judged as nonatrophic in this series, although partial atrophy is visible between malleus and long process of incus.

indicated.

The fascia press was not used, and fascia was probably thicker than it would have been had it been pressed. The fascia and perichondrium grafts were thinned sufficiently to allow correct positioning, and the grafts were not dried. All ears were examined repeatedly with the Zeiss OPMI-1 otomicroscope postoperatively, and photographic preoperative and postoperative records were made with the Brubaker-Holinger endoscopic camera in all but a few ears.

Atrophy was judged by the thin, translucent character of the graft. Grafts that maintained their fibrous quality appeared as thickened, pinkish to whitish areas in the graft site (see Figure, F).

I judged the microscopic appearance to be sufficient evidence of graft atrophy. In a few cases, the

RESULTS OF FOLLOW-UP

	Fascia Graft			*Perichondrium Graft*		
	Cholesteatoma	*COM*	*Total*	*Cholesteatoma*	*COM*	*Total*
No atrophy	6	2	8	8	4	12
Atrophy	33	2	35	7	1	8
Total	39	4	43	15	5	20

Data are numbers of ears.
COM — chronic otitis media.

atrophic nature of the graft was proven with the plain lens pneumatic otoscope and the otomicroscope. Pneumatic otoscopy is difficult and often impossible following tympanoplasty with canalplasty and endaural incisions.

Most of the ears with cholesteatomas were intubated at surgery, and ME ventilation was maintained throughout the period of postoperative follow-up for as long as possible. The presence or absence of the tube appeared to have no relation to the development of graft atrophy. Atrophy, beginning atelectasis, and even beginning cholesteatoma reformation were noted in some ears in which the ME tube had been extruded spontaneously between follow-up visits, as sometimes occurred as long as 2 to 4 years postoperatively (see Figure, A).

RESULTS

The results are summarized in the Table.

Fascia Grafts. Forty-three ears were grafted with temporalis fascia, and 35, or 80%, showed atrophy of part or all of the graft. In 4 ears, the entire graft atrophied. In 9 ears, one half or less of the graft area was atrophic. Time was a factor in the development of atrophy, since 32 atrophic grafts were inserted before 1987. The average follow-up period for all fascia grafts was 2.7 years.

Perichondrium Grafts. Twenty ears were grafted with perichondrium. All but one of the grafts were performed in 1987 and 1988. Twelve grafts did not atrophy, and eight ears showed some degree of atrophy. One graft was judged to have atrophied over 100% of the graft surface area, four atrophied over 50%, and three over 25%. Four of five grafts for simple perforations did not atrophy. One perichondrium graft did not show atrophy after an 8-year follow-up. The average follow-up period for all perichondrium grafts was 2.9 years.

CASE REPORTS

Case 1. A 40-year-old woman had a pars tensa posterosuperior margin retraction-type cholesteatoma that extended toward the sinus tympani region and partially eroded the long process of the incus. No preoperative photos were taken. In 1983 the retracted, atelectatic cholesteatoma matrix was removed by enlarging the posterosuperior bony canal wall, and a fascia graft was underlaid to close the defect in the posterior half of the TM. A polyethylene tube was inserted into the intact anterior TM.

Follow-up was poor, and when the patient returned in 1987, the ME tube had extruded and the posterosuperior grafted area was thin, atrophic, and retracted deep into the posterosuperior quadrant and inferior epitympanum, where it "shrink-wrapped" the long process of the incus and the stapes. Epithelial debris had accumulated in the stapes crura, indicating the onset of recurring cholesteatoma (see Figure, A).

Reintubation of the ME resulted in correction of the atrophic TM collapse (see Figure, B).

Case 2. A 41-year-old man had a deep posterosuperior pars tensa–type cholesteatoma confined to the ME. In 1987, the lesion was excised and grafted with perichondrium. The ME was intubated. The long process of the incus was eroded, and the incus was transposed over the stapes. At 6 months, the graft was well healed and the ME was aerated by an ME tube.

Two years postoperatively the ME vent was extruded, the perichondrium graft was 50% atrophied, and a thin, atrophic area of the reconstructed TM was retracted into the ME and the epitympanum (see Figure, C). Reintubation relieved the atelectasis, and the atrophic graft returned to the plane of the normal TM (see Figure, D).

Case 3. A 23-year-old woman had a history of recurrent secretory otitis media with multiple tube insertions throughout childhood. There was a large (80%) central perforation with stratified squamous epithelium lying on the medial surface of the TM remnants. The ossicles were intact (see Figure, E). A perichondrial myringoplasty was performed once the cholesteatomatous TM rests were removed.

Postoperatively, the graft healed without atrophy. But 2 years later the entire TM had collapsed onto the promontory, partially enveloping the long process of the incus and the malleus handle (see Figure, F). As might be expected, this patient was reluctant to have further intubations.

DISCUSSION

As the Table shows, 33 of 39 (85%) fascia TM grafts used in the treatment of ME cholesteatoma atrophied postoperatively — some in less than 2 years. Perichondrium, a tougher and more fibrous tissue, also atrophied, but to a lesser degree. Seven of the 15 grafts for cholesteatoma demonstrated various degrees of atrophy. These grafts have not been followed up for as long as the fascia grafts, and only follow-up over time will reveal their fate. Although these grafts seem to atrophy less frequently than fascia, case 2 demonstrates that while perichondrium grafts do not atrophy completely, localized atrophic areas can collapse medially when ME ventilation is faulty.

Case 3 demonstrates that the more fibrous perichondrium is not strong enough to prevent ME collapse when the ME is underventilated, despite the fact that the graft in this ear did not atrophy.

The cause of connective tissue graft atrophy is not apparent from this study. Plastic surgeons have long told us that skin grafts tend to scar, shrink, and atrophy, and it appears that the connective tissue TM grafts are no exception to this general rule.

Atrophic grafts will not become atelectatic if ME ventilation is normal. In this series most of the cases of atelectasis were corrected by simple ME intubation. We showed in 1969[11] and in 1984[12] that atelectasis can frequently be corrected by simple artificial ME intubation.

Practically all of the ears with cholesteatoma in this series were intubated at surgery. But because ventilation tubes extrude eventually, graft atrophy and atelectasis are a constant recurring threat to an otherwise good surgical result.

We should not forget that we are treating chronic otitis media and that poor ME ventilation is an underlying cause of some cholesteatomas and the chronic perforations as well as atelectasis. This underaeration is not ameliorated or affected in any way by TM grafting. In this study long-term follow-up and otophotography detected and documented the atrophic and atelectatic changes.

CONCLUSIONS

This study questions the effectiveness of the surgical treatment to strengthen atrophic TMs in ME atelectasis, since 80% of the fascia grafts and almost half of the perichondrium grafts used in this study for atelectatic cholesteatomas and chronic TM perforations atrophied postoperatively.

Lack of gasification, aeration, or ventilation remains the basic problem in ME atelectasis and in some types of cholesteatomas, and TM grafting and tympanoplasty will fail if the ME is not ventilated naturally or artificially.

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CLEARANCE FUNCTION OF EUSTACHIAN TUBE AND NEGATIVE MIDDLE EAR PRESSURE

HARUO TAKAHASHI, MD
KYOTO, JAPAN

IWAO HONJO, MD
KYOTO, JAPAN

MASAHIKO HAYASHI, MD
SHIGA, JAPAN

AKIHIKO FUJITA, MD
KYOTO, JAPAN

Two experimental studies were performed using 18 cats in order to elucidate the mechanism of the long-lasting course of otitis media with effusion. First, the middle ear (ME) pressure was monitored for 2.5 to 7 hours after filling the whole ME space with saline. On average, -150 mm H_2O of negative ME pressure was induced in 3.1 hours. Second, the residual volume of saline with antibiotics, which was put into the ME space 2 to 7 days before, was compared between the side on which tubal ventilatory function was abolished (resection of tensor veli palatini muscle and hamulus pterygoideus) and the opposite, control side. The percentage of the residual volume to the original volume put into the ME was significantly higher on the experimental side (Wilcoxon's ranking test, $t = 27.0$, $p < .05$), and in one ear on the experimental side, the ME pressure showed -150 mm H_2O just before the bulla was opened 2 to 7 days later. These results seem to indicate that tubal ciliary clearance function can induce negative ME pressure when there is fluid in the ME, and that the negative ME pressure induced by clearance of the ME fluid may disturb further clearance of the ME fluid. This condition may cause the long-lasting course of otitis media with effusion.

KEY WORDS — clearance function, eustachian tube, middle ear pressure, otitis media with effusion.

INTRODUCTION

The negative middle ear (ME) pressure observed in most ears with otitis media with effusion (OME) has been explained mainly with the "hydrops ex vacuo" theory.[1] According to this theory, air in the closed ME space is absorbed, and then serous transudate comes from the surrounding tissue because of the negative ME pressure that results when the eustachian tube (ET) is obstructed. However, there seem to be still several points that cannot be explained by this theory. First, clinical and experimental studies regarding ME pressure in ears with tubal ventilatory dysfunction have failed to reveal a progressive decrease in ME pressure.[2,3] Also, in spite of the fact that the entire ME space of chronic OME patients was proved to be filled with effusion, almost without any air space, by magnetic resonance imaging (MRI),[4] the ME still shows negative pressure in most OME patients.[5] One of the alternative possibilities suggested is that the ciliary and muscular clearance functions of the ET induce negative ME pressure when they expel fluid from the closed ME space.[6,7]

On the other hand, regarding the cause of the usual prolonged course of OME, as well as several contributions in the immunologic and bacteriologic fields such as detection of immune complex[8] and endotoxin[9] in the ME effusion, one interesting finding was that the ME effusion disappeared in a short time after myringotomy without suctioning of the effusion.[10,11] Because a sudden release of negative ME pressure is considered to be the biggest change of the ME condition in this case, the negative ME pressure also seems to be responsible for the prolonged retention of ME fluid.

These findings lead us to a hypothesis that negative ME pressure may be caused by the clearance function of the ET, and that the induced negative ME pressure, which usually cannot be released transtubally by OME patients,[12] should disturb further clearance of ME effusion. Thus, a deadlocked prolonged condition arises within the ME.

To test this hypothesis, two experimental studies were performed. One was to confirm whether negative ME pressure is induced by the ET ciliary clearance function when the whole ME space is filled with fluid. The other was to examine if transtubal clearance of the ME fluid is disturbed by the negative ME pressure induced by the clearance function per se when ET ventilatory dysfunction coexists.

MATERIALS AND METHODS

Study 1. Eleven adult cats (16 ears) with normal eardrums were used in this study. Under general anesthesia with ketamine hydrochloride (10 mg/kg, intramuscularly) and pentobarbital sodium (30 mg/kg, intraperitoneally), and under controlled respiration with room air through a tracheotomy, a polyeth-

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From the Department of Otolaryngology, Faculty of Medicine, Kyoto University, Kyoto, Japan.

REPRINTS — Haruo Takahashi, MD, Dept of Otolaryngology, Kyoto University, Sakyo-ku, Kyoto, 606, Japan.

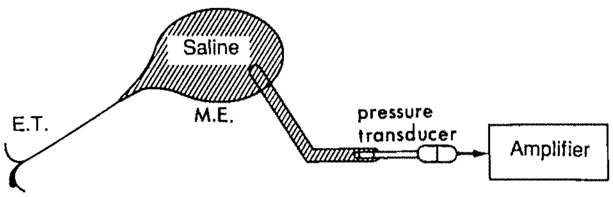

Fig 1. Scheme of experimental method in study 1. E.T. — eustachian tube, M.E. — middle ear.

ylene tube was hermetically connected to the tympanic bulla through the cervical approach. All the air space within the ME cavity and the connected tube was filled with physiologic saline, and the other side of the tube was connected to a pressure sensor (Mikro-tip, Miller PC-330, 3F) placed at the same horizontal level as the bulla so that the monitoring pressure precisely reflected the ME pressure (Fig 1). The ME pressures were monitored for 2.5 to 7 hours. In 3 ears, the mucosa of the ET was destroyed by applying 0.02 mL of 20% silver nitrate to the ET, and in another 2 ears, the tympanic orifice of the ET was obstructed with dental cement.

Study 2. Seven adult cats (14 ears) with normal eardrums were used in this study. Under general anesthesia with ketamine hydrochloride (10 to 15 mg/kg, intramuscularly) and pentobarbital sodium (10 to 15 mg/kg, intraperitoneally), the tensor veli palatini muscle was transorally transected and completely separated, and the hamulus pterygoideus was also extirpated on one side. The bilateral tympanic bullae, exposed through the cervical approach, were filled with physiologic saline with antibiotics through a small hole made in each bulla. The holes were closed with bone wax, and all the wounds were sutured aseptically. Hydrocortisone (50 mg, intraperitoneally) was administered just after these operative procedures so that the ciliary function of the ME and ET would not be affected by the inflammation of these wounds. The tympanic bullae were opened 2 to 7 days later, and the amounts of the residual saline on each side compared. In 1 ear with abolished ET ventilatory function, the ME pressure was measured transtubally with a microtip catheter pressure sensor (Mikro-tip) 2 days after the instillation of saline.

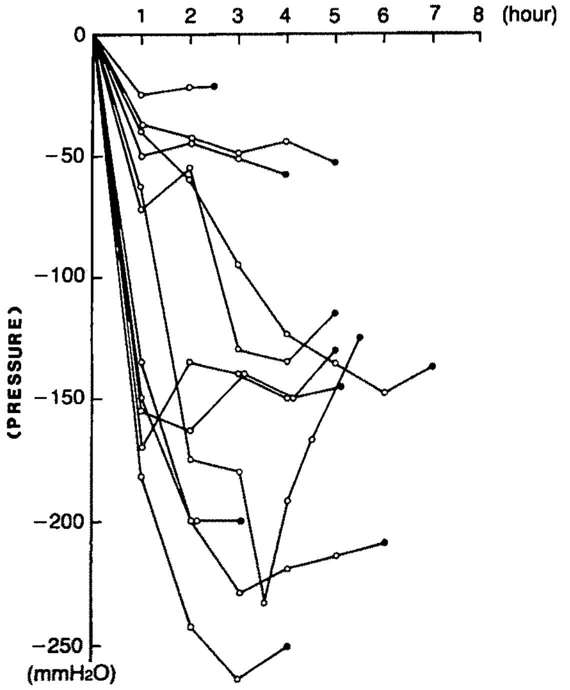

Fig 2. Chronologic change of middle ear pressure in study 1.

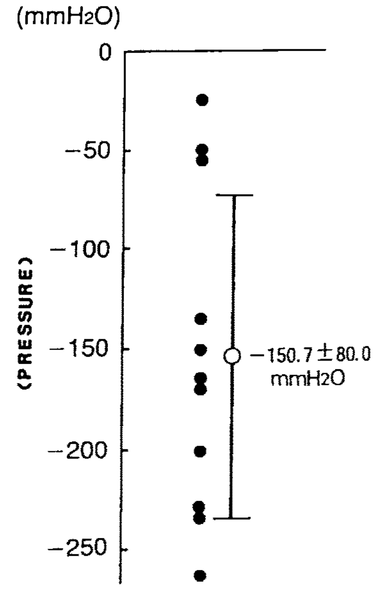

Fig 3. Maximal negative middle ear pressure in study 1.

RESULTS

Study 1. Chronologic changes in ME pressures in the 11 ears with intact ETs are shown in Fig 2. In 1 to 6 hours, maximal negative pressures of −25 to −265 mm H2O were induced. The ear with the quickest response showed −180 mm H2O of negative ME pressure at 1 hour, and negative ME pressures lower than −200 mm H2O were seen in 4 ears at 2 to 3.5 hours. Maximal negative ME pressure was found to be −150.7 ± 80.0 mm H2O at 3.1 hours on average (Fig 3). These negative ME pressures then tended to diminish within a few hours, restabilizing at approximately −150 mm H2O. When the closed space was opened after the experiment, the pressure returned to approximately 15 mm H2O in all the ears examined. In the 3 ears in which the ETs were destroyed with silver nitrate and the 2 ears in which the ETs were obstructed with dental cement, the maximal negative ME pressures induced were −25 mm H2O (mean, −14.0 mm H2O) and −16 mm H2O (mean, −13.0 mm

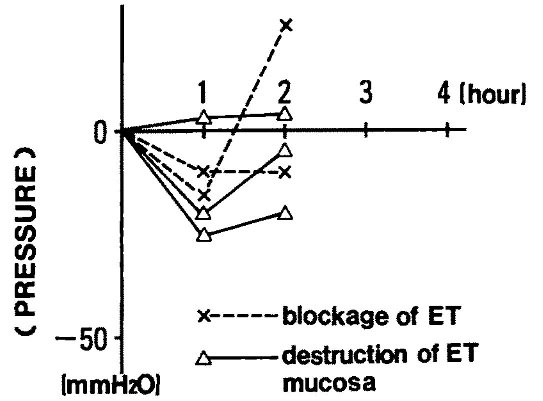

Fig 4. Chronologic change of middle ear pressure in control ears in study 1.

H_2O), respectively (Fig 4).

Study 2. The amounts of residual saline in the ME at 2 to 7 days are shown in the Table. One ear on the control side (No. 6) was excluded from the study because of occurrence of otitis media during the experimental period. The residual volumes of the fluid in the ME were more than 50% of the originally instilled volume in five of the seven ears on the operated side, whereas on the control side, no fluid was observed in four of the six ears, and the residual volumes were less than 20.0% and 22.2% in the remaining two ears. The difference in the residual volume percentages between the two groups was significant (Wilcoxon's ranking test, $t = 27.0$, $p < .05$), indicating that ears with ventilatory dysfunction of the ET showed a significant delay in excretion of ME fluid.

The ME pressure measured in one ear on the operated side (No. 7) before opening the tympanic bulla was found to be −150 mm H_2O (Fig 5), despite the opposite ear's showing a type A tympanogram at the same time.

DISCUSSION

In study 1, because comparatively deep anesthesia prevented the animals from swallowing during the whole period of the experiment, the ME pressures induced did not appear to be affected by transtubal ventilation or the muscular pumping function of the ET.[7]

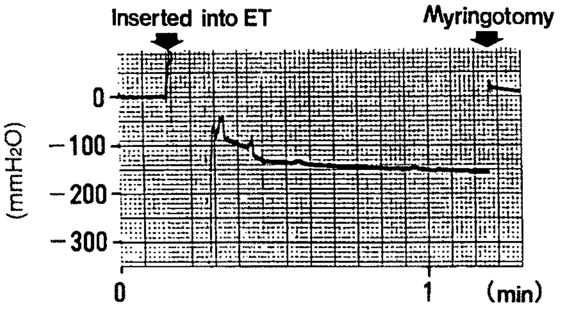

Fig 5. Middle ear pressure on experimental side of animal 7. It was −150 mm H_2O and returned to approximately 0 mm H_2O with myringotomy.

Furthermore, in the control animals, in which the ET was obstructed or its ciliary epithelium destroyed, no consistent negative ME pressure was induced. The negative ME pressures observed in this experiment, therefore, were considered to be induced by ciliary propulsion of fluid from the closed ME space. Murphy[6] reported that −166 mm H_2O (average) of maximal negative ME pressure was induced by the ciliary function of the ET in 53 minutes on average when mucus was introduced in the ME in cats. The value of the maximal negative ME pressure he obtained is quite close to ours, but the time until the negative ME pressure became maximal was shorter than ours. This discrepancy in time may be due to a difference in the experimental method: in his experiment, there would have been some air space left in the ME, which may have allowed another factor to affect the ME pressure, such as ME gas exchange. On the other hand, the similarity of the pressures in his and our experiments may indicate that the negative ME pressure induced by the tubal ciliary function is rather consistent, regardless of the volume of fluid within the ME cavity.

In study 2, we produced experimentally a condition of the ET similar to that of OME patients, in which the ventilatory function was almost totally abolished without much damage to the ciliary clearance function.[12] As a result, a significant delay in the clearance of ME fluid was observed on the experimental side. At the same time, in one ear on the experimental side, the ME showed a negative pressure (−150

CHANGE OF VOLUME OF SALINE IN MIDDLE EAR IN STUDY 2

Case No.	*Period (d)**	*Operated Side*		*Control Side*	
1	7	0.6 → 0.5 mL	(83.3)	0.6 → 0.0 mL	(0.0)
2	7	0.55 → 0.0 mL	(0.0)	1.0 → 0.0 mL	(0.0)
3	7	1.0 → 0.1 mL	(10.0)	0.75 → 0.0 mL	(0.0)
4	2	0.6 → 0.3 mL	(50.0)	0.5 → <0.1 mL	(<20.0)
5	2	0.55 → 0.3 mL	(54.5)	0.45 → <0.1 mL	(<22.2)
6	2	0.8 → 0.4 mL	(50.0)		
7	2	1.0 → 0.5 mL	(50.0)	1.0 → 0.0 mL	(0.0)

Number in parentheses indicates percentage of volume of originally instilled fluid that remains.

*Experimental period from instillation of saline into middle ear to measurement of residual saline.

mm H2O) that was quite close to the maximal negative ME pressure induced by the tubal clearance function in study 1. It is therefore conceivable that the ciliary clearance function was disturbed by the negative ME pressure induced by the transtubal clearance of the ME fluid when the ME pressure had reached around −150 mm H2O, and that the inability of the ET to release that negative ME pressure may have made this deadlocked condition irreversible.

From the results of these two studies, it was concluded that when both ME fluid and tubal ventilatory dysfunction exist, irreversible negative ME pressure can be induced by the ciliary clearance function of the ET, which could cause a long-lasting condition in which fluid and negative ME pressure coexist in the ME.

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GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

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CHONDROBLASTOMA OF THE TEMPORAL BONE

CASE REPORT AND LITERATURE REVIEW

MARK A. VARVARES, MD
MACK L. CHENEY, MD
MAX L. GOODMAN, MD
EMILY CEISLER, MD
WILLIAM W. MONTGOMERY, MD
BOSTON, MASSACHUSETTS

Chondroblastoma is a rare tumor of bone that represents approximately 1% of all primary bone tumors. In the temporal bone, only 33 have been reported. We present a case of chondroblastoma of the temporal bone, followed by a literature review and analysis of reported cases. We conclude that the best chance for a prolonged disease-free interval is total excision using a combined otolaryngologic and neurosurgical approach.

KEY WORDS — chondroblastoma, connective tissue neoplasms, temporal bone.

INTRODUCTION

Benign chondroblastoma is a rare tumor of bone that represents approximately 1% of all primary bone tumors. These tumors are most commonly found arising in the epiphysis of a long bone, with the femur, humerus, and tibia being the most commonly affected.[1]

Primary bone tumors of the cranial bones are considered rare, comprising 2% of all primary bone tumors.[2] A chondroblastoma of the temporal bone is an even rarer entity, with only 32 cases having been reported previously.[1-13]

We now present a case of chondroblastoma of the temporal bone that was referred for definitive treatment. Included is a comprehensive review of all cases reported to date, including symptoms, physical examination findings, radiographic data, treatment modalities, and outcome.

CASE REPORT

A 33-year-old man presented with a 1-year history of right-sided otalgia. Subsequently, he developed decreased hearing on the right with progressive dysequilibrium and headache. A slowly enlarging mass was noted in his right temporal area.

Initial evaluation at an outside institution revealed a mass in his right external auditory canal. A biopsy yielded diagnosis of granulation tissue. He was treated with enteral antibiotics, but noted no improvement in his symptoms. He then underwent treatment for presumed temporomandibular joint dysfunction with oral analgesics. Eventually, a computed tomography (CT) scan was done that showed a large lesion of the right petrous bone with extension into the middle cranial and infratemporal fossae (Fig 1). The lesion in the right external auditory canal was again submitted to biopsy, this time with a diagnosis of chondroblastoma. He was then referred to the senior author (W.W.M.)

At presentation, the patient complained of severe right-sided otalgia. Physical examination revealed a tender swelling over the right temporal and preauricular area. The right external auditory canal was occluded by a tumor. The patient's Weber examination lateralized to the left. The remainder of the findings on neurotologic examination, including cranial nerves, were unremarkable. Examination of the oral cavity showed painful trismus. The remainder of his head and neck examination was without evidence of any other masses. An audiogram was obtained that was essentially normal.

A magnetic resonance imaging (MRI) scan was performed and showed a large extradural lesion of the right petrous bone, with extension into the middle and infratemporal fossae. A preoperative cerebral arteriogram was consistent with an avascular mass without carotid compression or displacement.

Upon consideration of the tumor location, a combined one-stage procedure with neurosurgery was planned. In the operating room the patient was prepared for an intracranial-extradural, transcervical-transmastoid surgical approach with an extended parotidectomy incision that extended superiorly well

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From the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts.
REPRINTS — William W. Montgomery, MD, Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

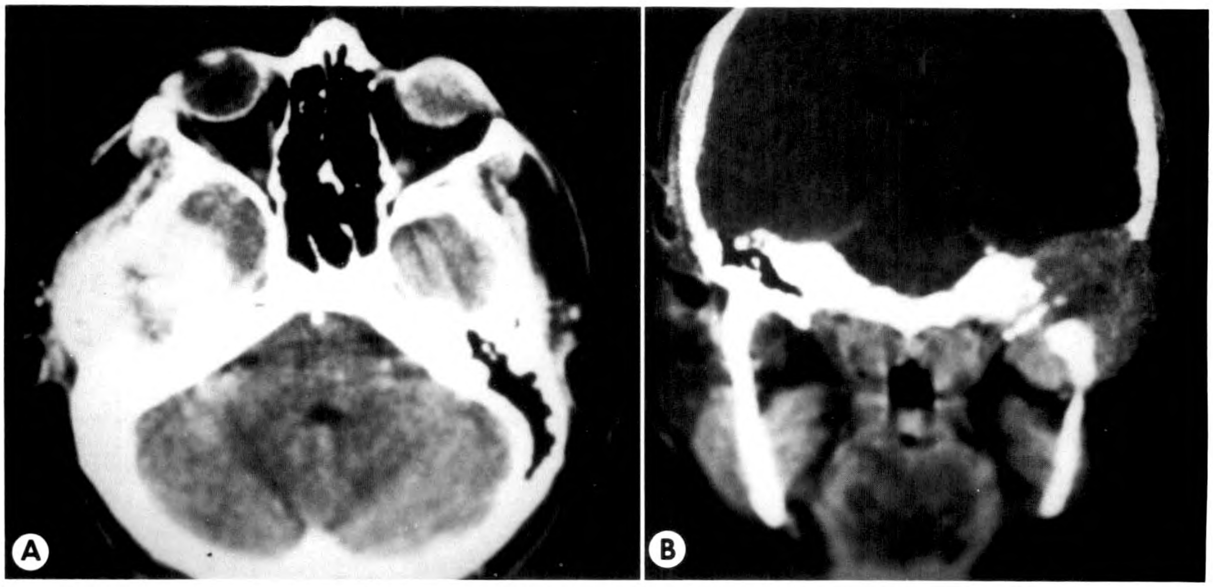

Fig 1. Contrast-enhanced computed tomograms of right temporal bone showing extent of bone destruction and encroachment of lesion on middle cranial fossa. A) Axial. B) Coronal.

into the temporal fossa and inferiorly into the neck along the anterior border of the sternocleidomastoid muscle (Fig 2A). As an initial maneuver, the common carotid artery and internal jugular vein were isolated so as to obtain proximal vascular control. An anterior skin flap was elevated over the parotid and the external auditory canal was transected and oversewn. The facial nerve was isolated at the stylomastoid foramen. A superficial parotidectomy was performed and the entire extratemporal facial nerve was identified and preserved. The lateral extent of the tumor was identified deep to the facial nerve. The mastoid cortex was exposed and a wide field mastoidectomy was performed. This exposure allowed the intratemporal portion of the tumor to be identified. The facial nerve was dissected as far as the geniculate ganglion. A middle fossa craniotomy was required to visualize the intracranial tumor. The medial resection margins and the labyrinthine portion of the facial nerve were fully visualized. During the extradural dissection, it was noted that the tumor was adherent to the dura but was able to be dissected free. As a final step in the resection, the zygomatic arch was transected. The condyle of the mandible and the infratemporal fossa contents were freed and the tumor was able to be delivered essentially en bloc. After hemostasis was obtained, a 6 x 6-cm tissue defect remained. This area included open air cells of the temporal bone, the internal auditory canal and associated nerves, and the trigeminal nerve (Fig 2B). A large fat graft harvested from the abdomen was used to obliterate the defect (Fig 2C). The wound was then closed in layers and drained. At the conclusion of the operation and just prior to wound closure, stimulation of the seventh cranial nerve at the internal auditory canal showed it to be intact.

Postoperatively, the patient recovered well. There was no evidence of cerebrospinal fluid leak, and the preoperative pain was relieved. The patient developed a temporary facial paresis that improved. An MRI scan with gadolinium and CT performed 2 years postoperatively revealed no evidence of recurrent or residual disease (Fig 3).

Pathology examinations of the resected tissue showed a chondroblastoma tumor involving the temporomandibular joint, petrous temporal bone, and bony ear canal with nodular extensions into soft tissues. Histologically, the cellular features were characteristic of chondroblastoma neoplasms (Fig 4).

LITERATURE REVIEW

Thirty-two cases of chondroblastoma of the bony ear canal with extensions into temporal bone have been reported, and 29 had detailed data.[1-10,12,13] The 29 patients with detailed data and our patient are represented in the discussions.

Age and Sex Distribution. The ages of patients reported ranged from 2.9 years to 70 years of age. If the patient that was 2.9 years of age is excluded, the median age within the group was 43.8 years.

The sex incidence was 21 males and 9 females for a male to female ratio of 2.3:1. The age range for the males was 16 to 66 years, and for the females it was 2.9 to 70 years.

Presenting Symptoms. Twenty-six patients had a detailed description of presenting symptoms. The

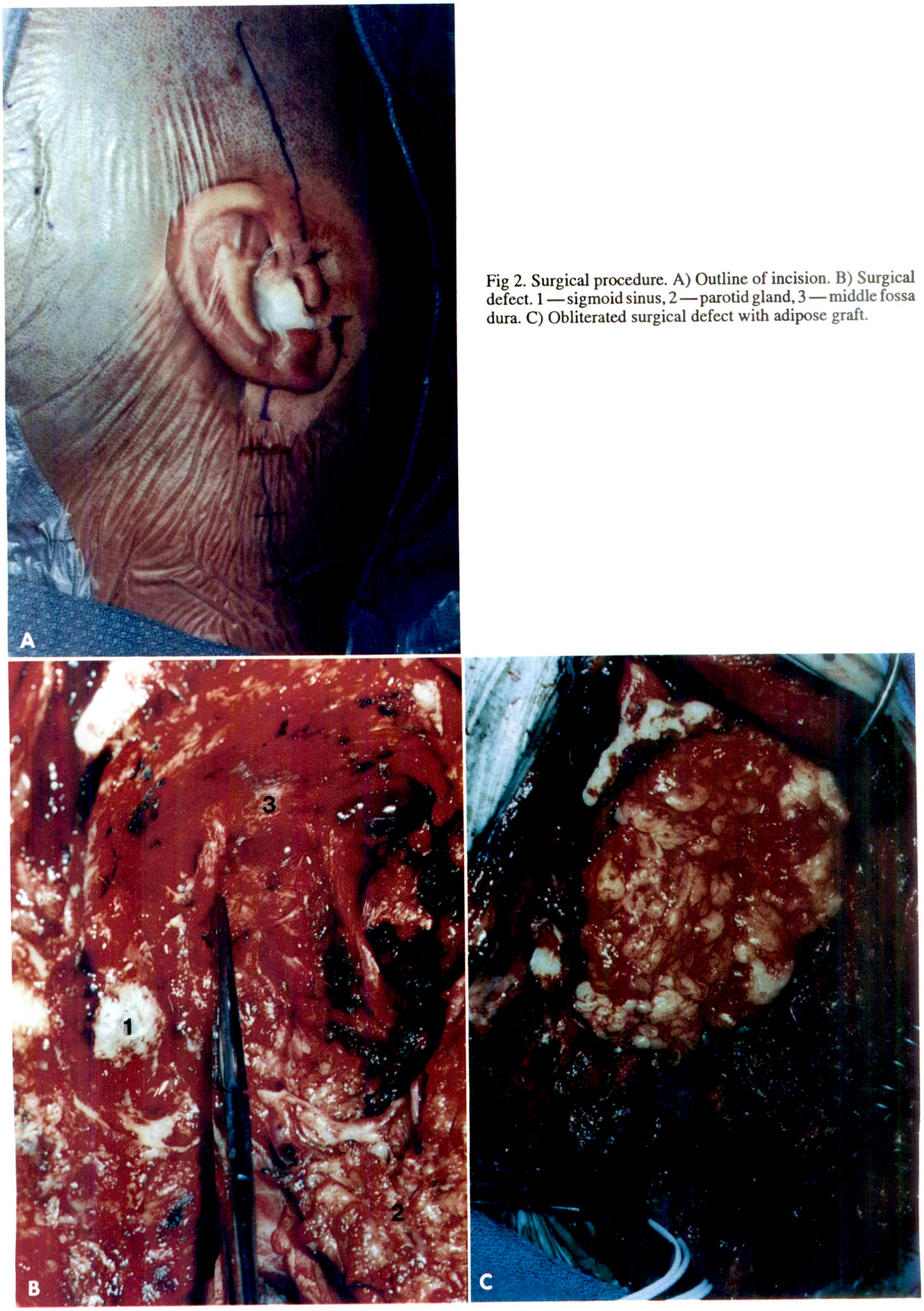

Fig 2. Surgical procedure. A) Outline of incision. B) Surgical defect. 1 — sigmoid sinus, 2 — parotid gland, 3 — middle fossa dura. C) Obliterated surgical defect with adipose graft.

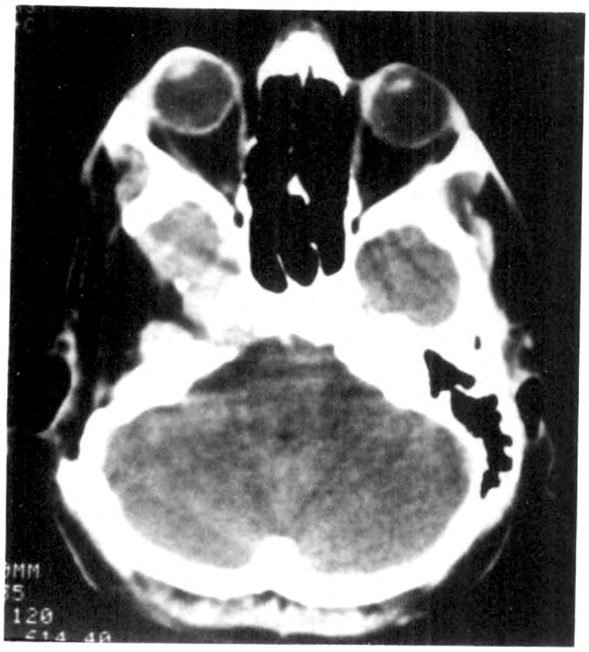

Fig 3. Axial computed tomogram showing obliterated surgical defect and no evidence of recurrent disease.

most frequent presenting symptoms are listed in Table 1. Symptoms that were most prominent were hearing loss, otalgia, tinnitus, and a mass sensation in the ear.

Most patients averaged two of the listed presenting symptoms, with a range of one to five. The average duration of symptoms prior to seeking medical attention was 12.5 months, although one patient reportedly had symptoms for 30 years; the range was from 2 months to 30 years.

TABLE 1. PRESENTING SYMPTOMS

Symptoms	*No. of Pts*
Hearing loss	13
Otalgia	8
Tinnitus	6
Mass	5
Vertigo or dysequilibrium	5
Aural fullness or blocked ear	4
Headache	4
Seizures	2
Pain	1
Temporomandibular joint arthralgia or dysfunction	1
Coma	1
Facial numbness	1

Physical Findings. Fourteen of the 29 patients had documented physical findings. The physical findings, in order of decreasing frequency, and the number of patients with each finding are listed in Table 2. The predominant alteration was a mass in the external auditory canal.

Radiographic Data. Radiographic examinations reflected equipment available at the time of presentation. These include plain films, tomograms, CT, and MRI. Eight patients had plain films performed. The temporal bone lesions were described as osteolytic (two patients), destructive (two), cystic (two), erosive (one), and multichambered with marginal sclerosis (one). Five patients had tomograms, with the lesions described as normal (one), destructive (three), and erosive (one). Eight patients had CT performed. The lesions were described as soft tissue with spotty central calcifications (one), normal (one), soft tissue

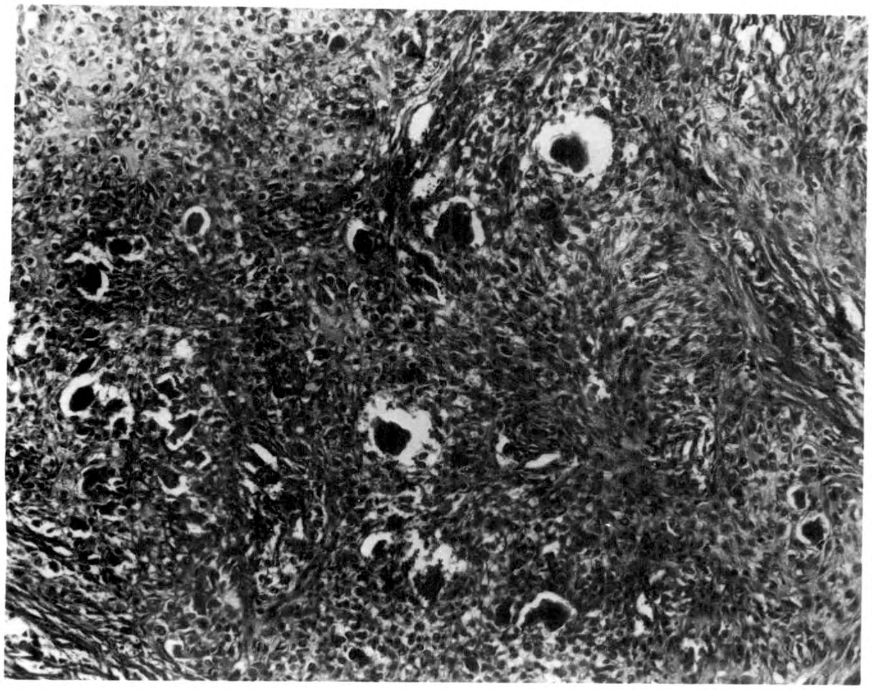

Fig 4. Photomicrograph of resected tissue.

TABLE 2. EXAMINATION FINDINGS

Findings	Patients (N = 14) No.	%
Mass in external auditory canal	10	71
Nontender temporal mass	3	21
Tender temporal mass	2	14
Papilledema	2	14
Altered mental status	2	14
Tenderness	1	7
Trismus	1	7
Nystagmus	1	7

TABLE 4. COMPLICATIONS IN FIVE PATIENTS

Complication	Type of Treatment Used
Conductive hearing loss	Total excision
Temporary cerebrospinal fluid leak, deafness, facial paralysis	Total excision
Temporary facial paralysis	Total excision
Radionecrosis of auricular cartilage requiring amputation	Radiotherapy (64 Gy)
Hearing loss	Total excision and radiotherapy (60 Gy)

mass with intracranial shift (two), lytic lesion (one), sharply demarcated solitary sclerotic lesion (one), destructive (one), and expansile (two). Two patients had MRI performed. Both of these lesions were reported as an expansile mass within the temporal bone.

Five patients had preoperative arteriograms. One showed a tumor blush, and the rest showed no evidence of a vascular mass.

Treatment. The treatment modalities in the previously reported cases were total en bloc excision, curettage, irradiation, and irradiation combined with surgical excision. The most effective modality appears to be total excision with or without irradiation. The number of patients in each group, as well as the length of follow-up and the presence or absence of recurrence, is listed in Table 3.

Complications of Treatment. Five patients had complications, and they are listed in Table 4, along with the initial type of treatment used. Hearing loss was the predominant complication. There have been reports of postirradiation sarcoma for treatments of other tumors and chondroblastomas in other sites, but this has not occurred in temporal bone chondroblastoma treatments.[14-16] Metastatic chondroblastoma from the temporal bone has not been reported.[15,16]

DISCUSSION

Chondroblastoma, a rare tumor, represents less than 1% of primary bone tumors[11] and occurs predominantly in the epiphyseal area of long bones. They are more common in the second decade, with a male to female ratio of approximately 2:1.

The temporal bone chondroblastoma presents at an older age than other sites, with an average of 43.8 years. The male to female ratio is 2:1.

The pathogenesis of chondroblastoma is uncertain. In long bones, it has been suggested that the chondroblastoma originates from the cells of the endochondral plate. Another theory proposes origin from reticulohistiocytes or related cells. Electron microscopic studies have concluded development from "normal cartilage cells to an altered local environment rather than an intrinsic alteration of cartilage cells per se."[11(p33)] Other electron microscopic studies have concluded origin from cartilage-forming matrix cells.[11]

The endochondral origin for portions of the temporal bone and the potential for rests of cartilaginous cells may allow this lesion to develop, with the appropriate initiating event. Similar theories have been proposed for the development of chondrosarcoma, which may arise de novo in the temporal

TABLE 3. TREATMENT GROUPS

Treatment	No. of Pts	No. of Pts With Follow-up	Length of Follow-up	No. of Pts NED
Total en bloc excision	8	7	0-63 mo (average, 27 mo)	7/7*
Curettage or incomplete excision	13	10	0-9 y (average, 3.4 y)	9/10†
Radiotherapy (64 Gy)	1	1	8.5 y	1/1
Curettage and postoperative radiotherapy (20 Gy)	1	1	4.5 y	1/1
Total excision with preoperative (1 pt) or postoperative (2 pts) radiotherapy (60 Gy)	3	3	0-9 y (average, 7.5 y)	3/3§

NED — with no evidence of disease.

*One patient had curettage 1 month before total excision.

†Four patients required two procedures because of recurrent or residual disease.

§One patient had incomplete removal 11 months before complete excision.

bone.[17]

Temporal bone chondroblastoma malignancy has not been reported,[15,16] secondary to irradiation or in the form of metastasis.[14-16] The number of chondroblastoma patients receiving irradiation is small, and the potential for malignant transformation may not be adequately formulated.

The primary presenting symptoms were predominantly otologic, with hearing loss being the most common. This was followed in decreasing frequency by otalgia, tinnitus, mass lesions, dysequilibrium, aural fullness, and headache, as well as other, less common complaints. These symptoms are all consistent with a slowly enlarging lesion of the temporal bone. The benign nature of this lesion is supported by the delay in presentation of the patients. Most patients had symptoms that had developed 1 year prior to seeking medical attention.

The most common finding on physical examination was a mass, either in the external auditory canal or in the temporal area. A small percentage of patients presented with increased intracranial pressure as a result of their tumor, manifested as papilledema, altered mental status, or coma.

The radiographic modalities used to evaluate these lesions were based primarily on the techniques available at the time of presentation. Earlier studies used primarily plain films and tomograms, whereas the later series used both CT and MRI. It is our opinion that CT allows clear delineation of the extent of bony destruction and MRI shows the tumor-dura interface and aids in determining if the tumor has remained extradural. Cerebral arteriography may be required for assessment of invasion or displacement of the internal carotid artery, or of tumor vascularity, and facilitates balloon test occlusion of the ipsilateral internal carotid artery should there be concern over possible sacrifice of this vessel.

The reviewed cases of chondroblastoma of the temporal bone show that any of the modalities used thus far in the treatment may result in a prolonged disease-free interval. The data indicate that initial curettage of the lesion results in recurrences requiring secondary procedures before attaining a disease-free interval. Patients who underwent an en bloc resection or total excision of tumor had no evidence of recurrence at an average follow-up of 27 months. Irradiation used alone or in combination with curettage or total excision was equally effective in the small number of patients treated with it.

It is evident that en bloc removal of tumor with the possibility of multiple cranial nerve deficits is not essential to obtaining a prolonged disease-free interval. Total excision of all gross tumor with careful preservation of the important neurovascular structures at the skull base should be adequate treatment for this benign lesion. This is attainable with the present surgical skills and approaches to skull base surgery. Radiotherapy is not recommended for this lesion.

Our approach with this patient and to similar lesions of the temporal bone is as follows. After a complete history is taken, physical and neurotologic examinations are performed with radiographic and angiographic evaluations. Surgery is a combined procedure with neurosurgery. A transmastoid-transcervical approach by the otolaryngology team allows early control of the major vascular structures at the skull base, and the isolation of the tumor at the skull base with its intratemporal component. The neurosurgery team performs a temporal craniotomy using an extradural approach to obtain superior and medial margins and visualization of tumor and the critical structures in the middle fossa. This combined approach allows for relatively safe removal of all gross tumor while preserving the major neurovascular structures of the skull base. Adipose obliteration of the operative cavity with watertight closure helps to prevent postoperative cerebrospinal fluid leak. If the tumor cannot be removed from the dura with the dura remaining intact, this portion of dura may be resected and reconstructed with fascia lata or irradiated homograft dura.[9]

SUMMARY

A case of chondroblastoma of the temporal bone is presented with a literature review of similar cases. The appropriate treatment appears to be a combined otolaryngologic-neurosurgical excision after proper clinical and radiographic evaluations to allow the total excision of the tumor with minimal morbidity.

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ORGAN-LIMITED LARYNGEAL AMYLOID DEPOSITS: CLINICAL, MORPHOLOGICAL, AND IMMUNOHISTOCHEMICAL RESULTS OF FIVE CASES

GODBER SÖNKE GODBERSEN, MD
KIEL, GERMANY

J. FRIEDEMANN LEH, MD
KIEL, GERMANY

MARTIN L. HANSMANN, MD
COLOGNE, GERMANY

HEINRICH RUDERT, MD
KIEL, GERMANY

REINHOLD P. LINKE, MD
MARTINSRIED, GERMANY

Five cases of organ-limited laryngeal amyloid deposits with no evidence of systemic disease are reported in detail and classified immunohistochemically. In four of the five cases the amyloid reacted with anti-Aλ antibodies and in one case with anti-Aκ antibodies. Four of our five female patients had already passed the fifth decade of life. One was 11 years old. Hoarseness was the predominant symptom in four cases, in which we found amyloid deposits in the glottic area. Only one patient, with amyloid deposits in the aryepiglottic fold, complained of pain. The therapy of choice of idiopathic, localized, or organ-limited amyloid deposits without underlying disease may be local excision. In one of the cases reported in this paper, a laryngofissure was performed, and in another a partial laser resection was performed. No therapy was performed in three of our five cases. In the larynx, as in many other locations and only if possible, removal at intervals is more feasible than radical resection, because these amyloid tumors grow slowly.

KEY WORDS — amyloidosis, immunologic techniques, larynx.

Subepithelial extracellular deposits of amyloid in the larynx are not uncommon. It is estimated that fewer than 1% of the benign tumors in the larynx are amyloid tumors.[1,2] Numerous cases of organ-limited laryngeal amyloid deposits have been reported so far.[1-20]

Different types of amyloidosis have been distinguished, varying in chemical structure and clinical aspects:

1. Amyloid of immunoglobulin light chain origin (κ or λ) in idiopathic or myeloma-associated amyloidosis.
2. Amyloid A in reactive amyloidosis.
3. Familial amyloid of the transthyretin type, with point mutations.
4. Senile amyloid of the transthyretin type.
5. Hemodialysis-associated amyloid.

Several other types have been distinguished, as well. The application of immunochemical techniques has made classification on formalin-fixed tissue sections possible.[21-23]

We report on five cases of laryngeal amyloid deposits demonstrating similarities in clinical, histopathologic, and immunohistochemical features. For the otolaryngologist, it is important to recognize this disease by clinical symptoms and signs[19] and to thereby distinguish it from other tumors.

METHODS

Biopsies from the larynx were fixed in 10% paraformaldehyde. Specimens were embedded in paraffin. Three-micrometer sections were cut and stained with hematoxylin and eosin and Congo red according to Puchtler et al.[24] The sections were examined immunohistochemically as described elsewhere,[22,23,25] with application of primary antibodies against the known amyloid types listed above.[25] Characterization of the isotype of immune cells was attempted in case 1 with antibodies against immunoglobulin light chains (λ and κ). The binding of the antibodies to the amyloid deposits was recognized and visualized by the peroxidase-antiperoxidase technique using 3-amino-ethyl carbazol as a chromogene.[25]

CASE REPORTS

Case 1. This 49-year-old woman complained of a sore throat and continuous coughing. She was admitted to the department of otorhinolaryngology at the University of Kiel in 1987. The family and patient

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From the Departments of Otorhinolaryngology (Godbersen, Rudert) and Pathology (Leh, Hansmann), University of Kiel, Kiel, and the Max Planck Institute of Biochemistry, Martinsried (Linke), Germany. This study was supported by the Deutsche Forschungsgemeinschaft, Sonderforschungsbereich 207, grant G8, Munich, and DFG Li 247/7-2, Li 247/9-1.

REPRINTS — Godber Sönke Godbersen, MD, Oberarzt, HNO-Klinik der Universität Kiel, Arnold Heller Strasse 14, 2300 Kiel, Germany.

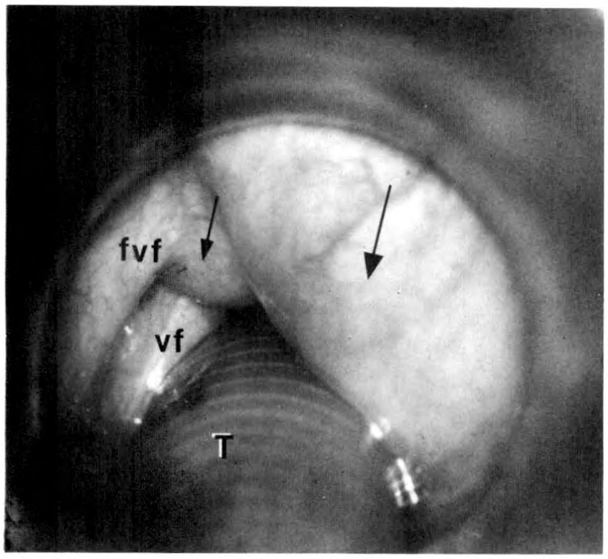

Fig 1. (Case 1) Organ-limited amyloid deposits of larynx visualized by direct laryngoscopy. Shows subepithelial swelling, mainly in right false vocal fold (fvf; arrows). T — resuscitation tube, vf — vocal fold.

history were noncontributory. She had had an appendectomy in 1958 and an abrasion of the uterus in 1977.

Laryngoscopic examination revealed a round, tumorlike subepithelial swelling at the anterior third of the right false vocal fold (Fig 1). Histopathologic examination revealed amyloid deposits. A biopsy, which was also performed on the right vocal fold and on the left false vocal fold, was negative for amyloid deposits. No other disease was found and no further therapy was performed. The patient was noncompliant with a request for follow-up.

Under the squamous epithelial layer, histology revealed a bandlike cellular infiltrate composed predominantly of plasma cells, lymphocytes, and macrophages. Some giant cells were detected as well. These giant cells were arranged focally around amorphous and sometimes globular material that was relatively homogeneous on hematoxylin and eosin staining (Fig 2). Some globules exhibited a radiating fibrillar structure.

Case 2. This 62-year-old woman was admitted to the department of otorhinolaryngology at the University of Kiel in 1987 complaining of a sharp pain in the tongue and throat. Her family history was unremarkable. She had had typhus and adnexitis 20 years before. A strumectomy was performed in 1971. Laryngoscopy revealed a swelling similar to a retention cyst on the right aryepiglottic fold and glossoepiglottic vallecula. Direct laryngoscopy and subsequent histopathologic examination of the biopsy specimen revealed the presence of amyloid deposits. No other disease could be found and no further therapy was performed. The patient was noncompliant with a request for follow-up.

Histologic examination showed a squamous epithelium at the surface. Only a few lymphoid cells were present below the basal epithelial layer. Distinct areas of homogeneous amyloid were identified with some capillaries and seromucous glands in between.

Case 3. This 11-year-old girl complained of gradually increasing hoarseness and was admitted to the department of otorhinolaryngology at the University of Kiel in 1970. The family history was unremarkable. Except for measles and rubella, the patient had never been ill before. Laryngoscopy revealed a discrete, reddish, polyplike swelling of the right false vocal fold. Direct laryngoscopy and histopathologic examination of the biopsy revealed the presence of

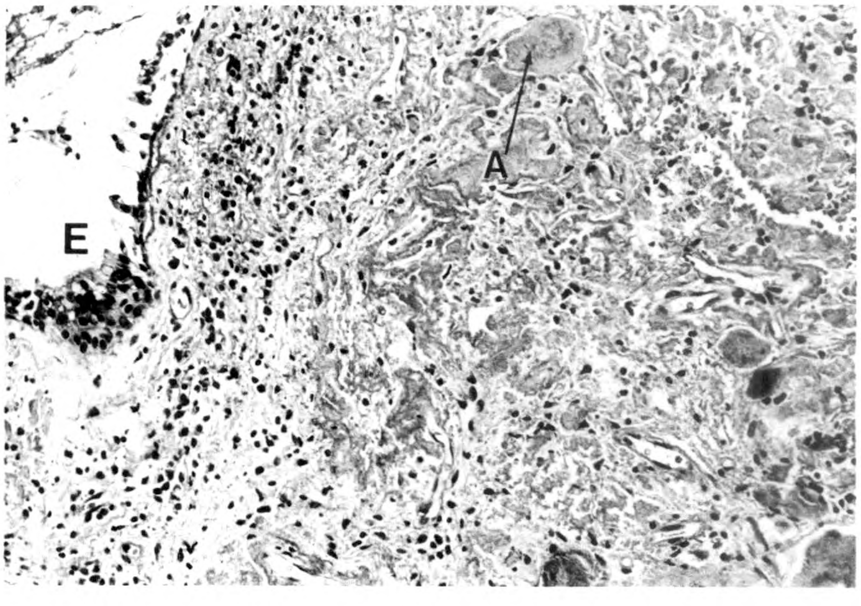

Fig 2. (Case 1) Histologic micrograph of biopsy specimen from larynx with amyloid (A; H & E, original x50). E — epithelial layer.

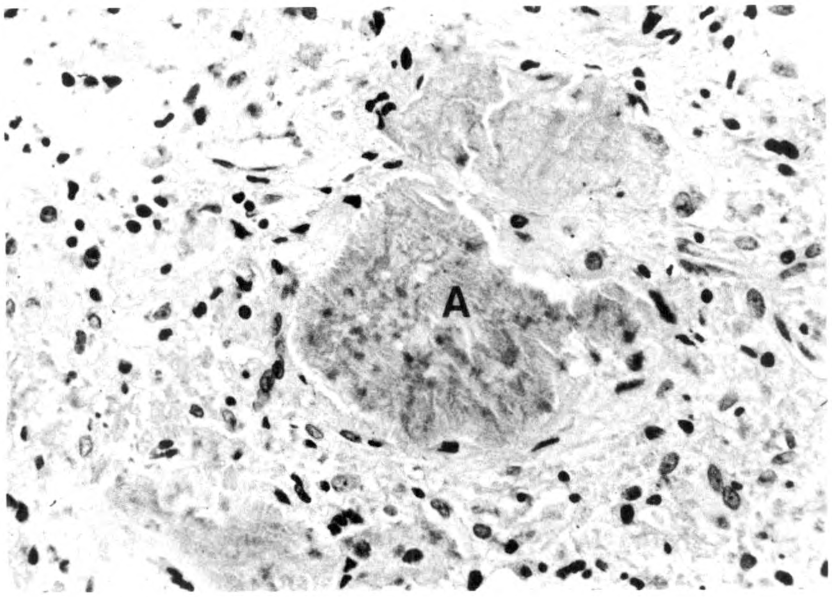

Fig 3. (Case 3) Amyloid deposits (A) surrounded by small lymphocytes, lymphoplasmacytoid cells, and macrophages in biopsy specimen from larynx (H & E, original x560).

amyloid deposits. No other disease could be found.

One year later, an incomplete local excision was performed, and 5 years later a laryngofissure, which had to be repeated 1 year later. No recurrence was seen on further follow-up.

A circumscribed amyloid deposit containing few lymphoid cells was found on histologic analysis of the fibrous tissue (Fig 3).

Case 4. This 57-year-old woman was admitted to the department of otorhinolaryngology at the University of Kiel in 1982. She complained of hoarseness that had been gradually increasing for 2 years. Her mother and one of her daughters had an unspecified kidney disease. That she had one nonfunctional kidney had been known for several years, but a diagnosis had never been made. The patient had a cholecystectomy in 1956. She also had osteoporosis of the dorsal spine and pain in the wrists. A whole body computed tomography scan revealed two dense masses in the liver resembling hemangiomas. There was no histologic evidence of amyloidosis in a biopsy of the rectum.

Laryngoscopy revealed a round, pink swelling of the mucosa in the anterior third of the left ventricle of Morgagni. Direct laryngoscopy and histopathologic examination of biopsy specimens from the left false vocal fold and the right and left ventricle of Morgagni revealed the presence of amyloid deposits. No therapy was performed. A checkup in 1986 revealed a slight swelling of the right false vocal fold. The patient complained of resistant cough and hoarseness.

Biopsies from the left false vocal fold and the right and left ventricles of Morgagni revealed clusters of homogeneous and clumplike amyloid deposits under the epithelial layer. Small clusters of lymphoid cells were located between the amyloid deposits. A few giant cells were found.

Case 5. This 61-year-old woman was admitted to the department of otorhinolaryngology at the University of Kiel in 1988. Severe hoarseness had been treated conservatively for more than a year without success. The family history was unremarkable. An appendectomy was performed in 1938 and a cesarean section in 1963. She had complained of dizziness for 8 years.

Clinical examination revealed a central defect of the right eardrum and a mixed hearing loss. A sensory hearing loss of retrolabyrinthine origin on the left side was ruled out. Indirect and direct laryngoscopy revealed a swelling of the right vocal fold. The right vocal fold was fixed medially. A computed tomographic scan displayed a tumor in the right vocal fold (Fig 4). A detailed internal examination revealed an

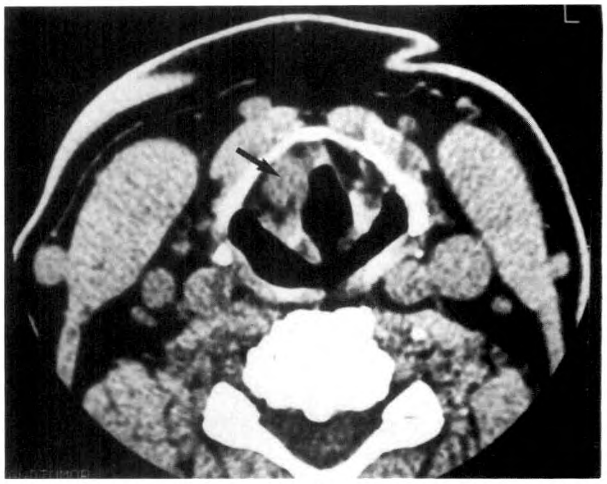

Fig 4. (Case 5) Computed tomogram of larynx with amyloid tumor mass (arrow).

OVERVIEW OF FIVE PATIENTS WITH LARYNGEAL AMYLOID DEPOSITS

Case	*Age (y)*	*Sex*	*Localization*	*Type*	*Therapy*
1	49	F	Right false vocal fold	Aλ	None
2	61	F	Right aryepiglottic fold	Aλ	None
3	11	F	Right false vocal fold	Aλ	LF
4	57	F	Left ventricle of Morgagni	Aλ	None
5	62	F	Right and left false vocal folds	Aκ	iLR

LF — laryngofissure, iLR — incomplete local resection with carbon dioxide laser.

enlarged right kidney without functional disturbance. A fatty liver was detected ultrasonographically. Rectal biopsy and biopsies of sternal and pelvic bone marrow provided no pathologic findings — in particular no amyloid deposits. An incomplete resection with a carbon dioxide laser was performed 2 years after diagnosis, in 1990. Histologic examination of the right vocal fold revealed homogeneous amyloid deposits, with some lymphoid cells, under an epithelial layer.

IMMUNOHISTOCHEMICAL RESULTS

Immunohistochemical features revealed immunoglobulin light chain amyloidosis in all five cases (see Table). In four of the five cases, the amyloid deposits reacted with anti–amyloid λ antibodies, while the other antibodies did not react. In one case, the amyloid reacted only with anti–amyloid κ antibodies. There was strong immunostaining of the amyloid deposits in three of the five cases; the reaction was moderate in only one case (case 3); and in case 5 the staining intensity was variable. Additional staining with antibodies against immunoglobulin free light chains could not reveal a monotypic immunoglobulin expression of the lymphoid cells in case 1, which had the densest lymphoid infiltrate.

DISCUSSION

Localized amyloidosis has been described in a variety of sites in the aerodigestive tract, including the orbit, nasopharynx, lips, floor of the mouth, tongue, larynx, and tracheobronchial tree.[19,20,26]

Laryngeal amyloid deposits are very rare in the pediatric age group.[10] We therefore draw attention to the fact that one of our patients was 11 years old when we saw her for the first time and she presented with amyloid deposits of the larynx. Four of our five female patients had already passed the fifth decade of life. The conspicuous female predominance in our five cases might be accidental, since male predominance has been described.[1]

Hoarseness was the predominant symptom in four cases with amyloid deposits of the glottic area. Only one patient, with amyloid deposits in the aryepiglottic fold, complained of pain. The clinical findings are in agreement with the other reported cases in the literature, the predominant feature being the localized and the organ-limited amyloid deposits.

The mechanisms that may lead to the formation and deposition of amyloid have not yet been elucidated. There are common features in all types of amyloid reported in the literature: 1) a distinctive and typical ultrastructure of amyloid fibrils on electron microscopy,[27] 2) a secondary structure with antiparallel beta sheet conformation,[28] and 3) an amyloid serum precursor that already has a high degree of beta sheet conformation.

Different protein groups have been seen to form amyloid fibrils, namely monoclonal immunoglobulin light chains (λ or κ) in idiopathic and myeloma-associated amyloidosis, amyloid A protein in reactive amyloidosis, and transthyretin (prealbumin) in the familial and senile forms of systemic amyloidosis.[29]

Immunohistochemistry provided the possibility of identifying all amyloid diseases when appropriate antibodies were available.[27] Of particular importance is the differentiation between immunocyte-derived and reactive systemic types.[21,25,27] With this method, amyloid in all our cases could be identified as immunocyte-derived, with the λ isotype in four cases and the κ isotype in one case. The latter case is to our knowledge the first identified κ isotype laryngeal, organ-limited amyloid.

Monoclonal plasma cell proliferations are the underlying disease, and the secreted immunoglobulin light chains are the precursors of the light chain type of amyloid. The monoclonal plasma cell proliferation may be malignant, such as a plasmocytoma, or benign. The proliferating plasma cells may often secrete immunoglobulins, resulting in monoclonal gammopathy or Bence Jones proteinuria. In spite of the predominance of immunoglobulins with κ light chains, the amyloid-forming light chain is instead of the λ type. In our cases, lymphocytes and plasma cells were found in the stroma within or around the amyloid deposits. Probably because of fixation and the kind of antibodies used, the attempt to demonstrate a monotypic immunoglobulin light chain production of these lymphoid cells failed in all five cases, although in one case, there was a dense infiltrate on mature plasma cells. Thus, there is no information as to the relationship of these cells to the amyloid. Examination of the bone marrow, which was performed in case 5 alone (our most recent case), did not reveal the presence of a plasma cell dyscrasia.

Preud'homme et al[30] demonstrated monoclonal plasma cell populations in systemic idiopathic (immunoglobulin light chain) amyloidosis by immunofluorescence. They were able to show a secretion of large amounts of free light chains, most often of the λ type, in every idiopathic or myeloma amyloidosis case, and the presence of light chain fragments in almost all of the 16 reported cases. In contrast, reactive amyloidosis revealed a normal distribution of bone marrow plasma cells. These data confirm that idiopathic amyloidosis belongs to plasma cell dyscrasia and emphasize the role of free light chains and light chain fragments in the pathogenesis of amyloid deposition.

Immunohistochemical differentiation and a new classification simplified the therapeutic approach.[21,28] The best therapy of idiopathic localized or organ-limited amyloidosis is thus far local excision. Eradicative laryngofissure or laryngotracheofissure, as reported by Watanabe et al[31] and performed 16 years ago in case 3, is possibly a very effective approach to avoid the recurrence of amyloid tumor and ensuing repeated resections in the same region. However, this approach may not be necessary when the tumor is growing very slowly. It must be kept in mind that even spontaneous regression is possible.[19] In many locations, as in the larynx, removal at intervals is more feasible than radical resection, and the procedure seems now to be favored. Resection with the carbon dioxide laser was described by McIlwain and Shepperd[12] and was performed in one of our cases without total resection of the tumor. As recurrence may become manifest after several years, long-term follow-up is recommended.[6] Development of a generalized amyloidosis did not occur in our cases, during a period up to 20 years in case 3, and to our knowledge has not been reported in the literature.

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20TH INTERNATIONAL CONFERENCE ON COCHLEAR IMPLANTS

The 20th International Conference on Cochlear Implants will be held June 23-25, 1993, at the Ritz-Carlton Hotel, San Francisco, California. For further information, contact University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; (415) 476-4251.

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THE JERUSALEM SYMPOSIUM ON SURGERY OF THE SKULL BASE AND ADJACENT MIDLINE REGION

The Jerusalem Symposium on Surgery of the Skull Base and Adjacent Midline Region will be held March 21-26, 1993, in Jerusalem, Israel. For further information, contact Dr F. Umansky, The Jerusalem Symposium on Surgery of the Skull Base and Adjacent Midline Region, PO Box 50006, Tel Aviv 61500, Israel; Telephone 972 3 5174571; Telex 341171 KENS IL; Fax 972 3 655674.

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NEW DEVICE FOR INTERDENTAL IMMOBILIZATION

BORIS O. DIVIS, MD, FRCSC
CAMPBELL RIVER, CANADA

The immobilization of a simple fractured jaw with arch bars is a time-consuming, laborious procedure. The alternative method of immobilization described here uses a precisely threaded, 22-gauge, malleable stainless steel wire and a threaded nylon nut. It affords the surgeon relative safety from accidental puncture trauma and makes the interdental immobilization a precise and speedy procedure.

KEY WORDS — alternative, arch bar, interdental immobilization, jaw fracture.

The Dimac wire (US Food and Drug Administration No. K910090; Dimac Medical Inc, Blaine, Wash) was developed as a simple and precise method of jaw immobilization that would afford greater safety to both the patient and the surgeon. It satisfies the surgical demands for simplicity of design and simplicity of application, while allowing direct observation of the dental occlusion (Fig 1).

Today, the common method of immobilizing a simple fracture with good dentition is by the application of Ivy loops or arch bars wired to individual teeth. Unfortunately, these are tedious and time-consuming methods, with the constant danger of trauma to the surgeon's fingers through the twisted wire ends, which need to be tucked away after they are trimmed. Twisting a wire around a tooth conveys very little information as to its tightness, and so there is a danger of avulsion if the pressure is too great.

To quote Wilson and Hohmann[1(p430-1)] from a paper on dental anatomy and occlusion,

> The structures responsible for maintaining the stability of the tooth are the gingiva, periodontal membrane, cementum and alveolar bone, which collectively are called the periodontium. It is obvious that during surgical procedures every effort must be made to preserve these supporting tissues. Damage to these structures may later result in tooth loss. For these reasons special precautions must be taken in the application of arch bars. All too frequently a large (number 24 or 26) wire is forced through the soft tissues of the interdental space. The tightening of this wire around a tooth may cause ischemic necrosis of the mucosa, periodontal membrane, and transverse fibers. If damage is extensive, tooth loss may result. It is much less traumatic to employ a loop of number 28 wire, which is passed around the tooth on a loop of dental floss,...

This gauge (28) calls for the application of a greater number of wires (16 or more), with increased likelihood of breakage, a longer operating time, and a greater chance of puncture trauma to the surgeon. If the wires are not sufficiently tight around the tooth at the time of operation, they will loosen and require retightening. Besides being unpleasant for the patient, retightening carries a constant danger of wire breakage and possibly a need for further anesthesia and surgery to replace the wires.

Dimac wires are a simple and speedy alternative, providing greater safety to both the patient and the surgeon. Each wire is made of 22-gauge malleable stainless steel that is threaded at one end and fitted with a threaded nylon nut that has a concave upper surface (Fig 2). There are 167 precision-cut threads per inch on the wire, and each full turn of the threaded nylon nut represents 0.152 mm (0.006 in) of movement along the wire. It is the precise cutting of the thread on the wire and the nut that is the heart of the system. It allows the surgeon to feel the tightness of the wire around the tooth and eliminates the chance of avulsion. The pressure of the nylon nut against the hooked wire sustains this tightness and provides stability. Only one tooth is required to create a wiring post, but there *must* be opposing dentition.

A further safety feature of the apparatus lies in the design, which uses nylon for the nut, causing it to strip if the pressure is too great. If this should happen, the wire remains in place and only the nut has to be replaced.

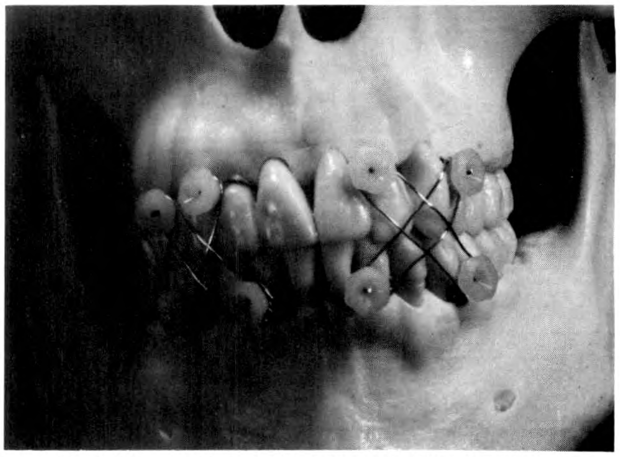

Fig 1. Dimac wires and interdental wiring in place.

REPRINTS — Boris O. Divis, MD, FRCSC, Suite 414, 1180 Ironwood St, Campbell River, British Columbia V9W 5P7, Canada.

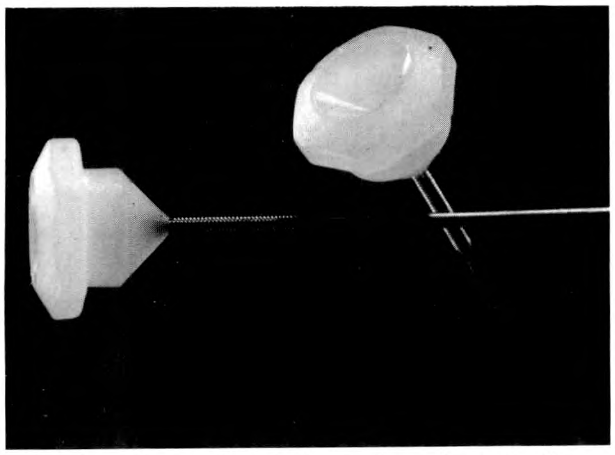

Fig 2. Close-up view of Dimac wire and nut showing precisely cut thread on wire and concavity of nut.

The wire is applied by being passed between adjoining teeth from buccal to lingual and back to the buccal surface through the next interdental space, encircling the tooth (Fig 3A). After the nylon nut is snugged against the teeth, it is unwound approximately 10 turns, and the distal end of the wire is brought medially and clockwise around the proximal end. It is then turned sharply on itself to create a tight hook, and the excess wire is snipped off (Fig 3B). The nut is then tightened down, and any excess wire protruding through the center of the nut is trimmed off in the concavity so that it does not irritate the mucosa. Because it is applied at right angles to the tooth, the wire remains firmly applied and does not loosen.

Up to eight wires may be used to immobilize a jaw, with a greatly reduced application time. Specifically, the 1 to 2 hours required for arch bar application is reduced to 20 to 40 minutes for Dimac wires — providing economy in the use of operating room time and personnel.

Besides being used to provide intermaxillary fixation for simple jaw fractures with good dentition, Dimac wires may be used intraoperatively or postoperatively in orthognathic surgery, temporomandibular joint surgery, jaw resection, and plating procedures. They also allow horizontal stabilization of jaw fractures by the application of interdental wires across adjoining teeth.

Postoperative adjustment is minimal and, if needed, requires only a fractional turn of the nut. There is no wire breakage or discomfort to the patient, as can happen with the postoperative adjustment of arch bars.

Removal of the wires is possible without anesthesia and consists of unscrewing the nylon nut and unhooking the loop of wire, which is then clipped off close to the tooth. The remaining wire is pushed backward and removed from the lingual aspect of the tooth (Fig 3C).

In 30 cases of simple jaw fractures with good dentition that were treated with this method of fixation, one patient required a wire to be tightened by a quarter turn of the nut. Two patients complained of irritation of the mucosa, and this was cured by the application of dental wax. In all cases there was minimal damage to the gingiva at the time of removal of the wires, with return to normal appearance within a week. None of the patients suffered damage to their teeth.

Dimac wires are manufactured in the United States and are sold in sets of 10 wires, including a nut driver, for $79.

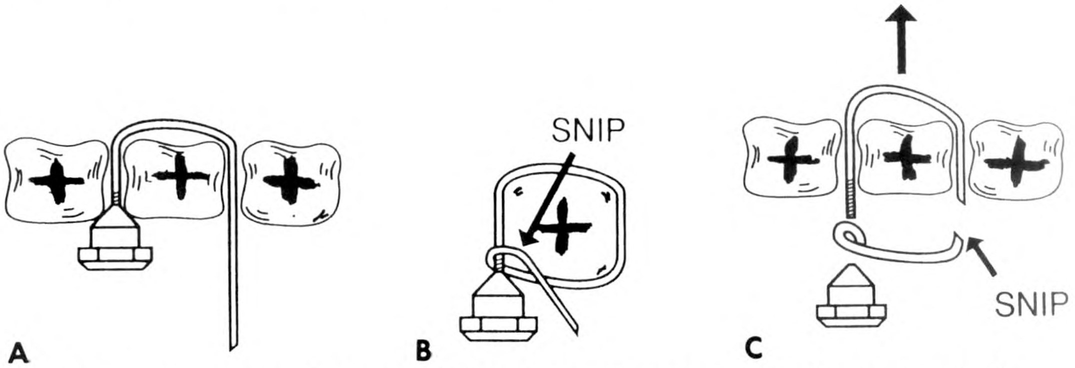

Fig 3. Procedure. A) Pass wire between adjoining teeth from buccal to lingual and back to buccal surface through next interdental space to encircle tooth. B) Snug nut against teeth and unwind it approximately 10 turns. Bring distal end of wire medially and clockwise around proximal end. Turn it sharply on itself, tighten down nut, and snip off any excess wire in concavity. C) To remove wire, unscrew nut and unhook loop of wire. Snip off close to teeth. Push remaining wire backward and remove from lingual aspect.

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CAROTID ARTERY RESECTION FOR HEAD AND NECK CANCER

MICHAEL D. MAVES, MD
ST LOUIS, MISSOURI

MATTHEW D. BRUNS, MD
ST LOUIS, MISSOURI

MICHAEL J. KEENAN, MD
CHICAGO, ILLINOIS

Occasionally, the head and neck surgeon encounters a patient whose malignancy involves the carotid artery. In these patients, curative or palliative surgery may require excision of the common or the internal carotid artery. However, the high complication and death rates dissuade many surgeons from undertaking carotid artery resection. This study reviews the outcomes in 20 patients treated between 1979 and 1985 at the Department of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, with resection of the carotid artery for head and neck cancer. The carotid artery was electively resected in 16 patients, while 4 patients underwent emergent carotid artery ligation. In the group of patients studied the stroke rate was 25%, the death rate 20%, and the combined stroke and death rate 30%. Of the patients who survived the procedure, all but 1 died of complications caused by tumor recurrence. These results are discussed, and compared with results from other studies.

KEY WORDS — carotid artery, head and neck cancer, stroke.

INTRODUCTION

Elective carotid artery resection is a controversial issue in the treatment of patients with advanced malignancies of the head and neck. Tumor adherence or invasion of the carotid artery may require carotid resection for control of disease. However, the significant risks of stroke and death, as well as the low cure rate, deter many surgeons from electively resecting the carotid artery.[1] Unfortunately, there are few alternatives. Failure to fully resect the segment of the carotid involved with tumor may result in tumor recurrence or death from carotid rupture.

Two primary situations require resection of the carotid artery. First, elective resection is necessary in some cases in which cancer has invaded the artery. The carotid is resected because of the high risk of potential rupture that exists if the artery is allowed to remain intact. Second, carotid artery resection is necessary to control hemorrhage from the artery. In these cases, the carotid artery is emergently resected or ligated after carotid rupture has already occurred.

This study reviews the postoperative outcomes in 20 head and neck cancer patients treated with resection of the internal or common carotid artery. The stroke and perioperative death rates are compared with those in other studies in an attempt to assess resection of the carotid artery as a viable option in these patients.

MATERIALS AND METHODS

From 1979 to 1985, 20 head and neck cancer patients underwent resection of either the internal or the common carotid artery at The University of Iowa Hospitals and Clinics. This group included 17 men and 3 women, with a mean age of 55, ranging from 30 to 70 years of age. As listed in Table 1, the primary tumor originated in the pyriform sinus in 5 patients and in the larynx in 5 other patients. Other primary tumor sites included the base of the tongue, nasopharynx, tonsillar fossa, oropharynx, and esophagus. In 2 patients, the primary tumor site could not be determined.

Sixteen of the patients underwent elective resection of the carotid artery, either because of tumor invasion or to prevent carotid rupture. Four patients required emergent ligation and resection of the carotid artery after rupture of the artery had already occurred.

Retrospective chart reviews were carried out to determine the long-term outcomes in this group of patients. Complications resulting directly from re-

TABLE 1. PRIMARY TUMOR SITE OF PATIENTS WITH CAROTID ARTERY RESECTION

Tumor Site	*No. of Cases*
Larynx	5
Pyriform sinus	5
Base of tongue	3
Nasopharynx	2
Undetermined	2
Oropharynx	1
Tonsil	1
Esophagus	1

From the Department of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, Iowa City, Iowa.

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REPRINTS — Michael D. Maves, MD, St Louis University Medical Center, 3635 Vista at Grand, PO Box 15250, St Louis, MO 63110-0250.

TABLE 2. COMPLICATIONS OF CAROTID ARTERY RESECTION IN HEAD AND NECK CANCER PATIENTS

Patient	*Age*	*Sex*	*Treatment*	*Complications (Days Postoperatively)*	*Cause of Death*	*Survival*
1	36	M	Elective		Respiratory failure	16 mo
2	66	M	Emergency	Stroke (34), perioperative death	Cerebrovascular accident	37 d
3	62	M	Elective	Stroke (8), SIADH, pneumonia, perioperative death	Cerebrovascular accident	22 d
4	52	M	Elective		Cardiopulmonary arrest	10 mo
5	45	F	Emergency		Respiratory arrest	4 mo
6	54	M	Elective	Seizure, stroke (6)	Lung metastasis	10 mo
7	66	M	Elective	Pneumonia (3)	Septic shock	35 d
8	61	F	Elective	Meningitis	Cardiopulmonary arrest	39 d
9	45	M	Elective		Lactic acidosis	5 mo
10	60	M	Elective		Respiratory arrest	8 mo
11	48	M	Elective		Tumor recurrence	33 mo
12	48	F	Elective	Fistula	Lung metastasis	12 mo
13	51	M	Elective	Fistula (20)	Cardiopulmonary arrest	14 mo
14	30	M	Elective			21 mo*
15	53	M	Emergency		Cerebrovascular accident	4 mo
16	74	M	Elective	Stroke (4)		34 mo*
17	55	M	Elective	Stroke (1), perioperative death	Cerebrovascular accident	7 d
18	64	M	Emergency	Blindness (4), fistula (6), perioperative death	Respiratory failure	7 d
19	70	M	Elective	Blindness (3)	Respiratory arrest	7 mo
20	63	M	Elective		Myocardial infarction	9 mo

SIADH — syndrome of inappropriate secretion of antidiuretic hormone.

*Lost to follow-up.

section of the carotid artery were identified and compared with the findings of other authors. In addition, the mean life expectancy of our patients following carotid artery resection was compared with the results given in similar studies to assess the benefit of this procedure.

RESULTS

Table 2 lists the patient age and gender, the circumstances under which carotid artery resection was performed, complications, and survival. The most common complication was stroke, with an overall incidence of 25%. Five patients suffered strokes postoperatively, three of whom died before being discharged from the hospital. Of the other two stroke victims, one survived for 10 months after carotid artery resection, eventually dying with tumor metastasis to his lungs; the other survived 34 months without clinical evidence of tumor recurrence, after which he was lost to follow-up.

The timing of stroke following carotid artery resection varied dramatically in our patients. One suffered a stroke postoperatively within the first 24 hours, three suffered strokes within the first 2 weeks, and one suffered a stroke 34 days following surgery.

In this study, we define perioperative death as occurring after surgery and before the patient's discharge from the hospital. Four patients died perioperatively as a direct result of their carotid artery resection. As stated earlier, three of those were patients who suffered strokes. The other patient, who required emergency resection of the carotid artery, developed blindness of his right eye caused by an embolus to the central retinal artery. He died of respiratory failure on the seventh postoperative day. Thus, we experienced a 20% incidence of perioperative death as a direct result of carotid artery resection. The two other perioperative deaths (one on the 35th postoperative day and one on the 39th) were caused by infections: one case of sepsis and one case of meningitis. Because these perioperative deaths did not result from carotid artery ligation, they are not included as complications of the resection. Combining the incidence of stroke and death in our study gives a 30% risk of either suffering a stroke or dying perioperatively as a direct result of carotid artery resection.

The patients in our study suffered other complications from carotid artery resection as well (Table 2). Three patients developed pharyngocutaneous fistulas. Two patients acquired pneumonia, and one became septic and died in shock. Two patients developed postoperative blindness from embolization of the central retinal artery. The syndrome of inappropriate antidiuretic hormone secretion occurred in one patient as a direct complication of a stroke. Another patient experienced seizures.

TABLE 3. MORBIDITY AND MORTALITY RATES OF CAROTID ARTERY RESECTION IN HEAD AND NECK CANCER PATIENTS

			% of Patients		
Study	*Year*	*No. of Cases*	*Stroke*	*Death*	*Combined Stroke and Death*
Watson and Silverstone[2]	1939	20	45	55	65
Moore and Baker[3]	1955	88	45	31	45
Gandhi and Oppenheimer[4]	1962	10	20	20	20
Moore et al[5]	1969	151	39	29	
Shumrick[6]	1973	19	21	58	79
Martinez et al[7]	1975	18		44	
Heller and Strong[8]	1979	59	25	29	37
Atkinson et al[9]	1984	12	17	8	17
Present study	1992	20	25	20	30

In this study, the mean life expectancy following carotid artery resection was 9.6 months. Of the 14 patients who survived beyond the perioperative period, 13 died because of tumor recurrence. A patient who died of a myocardial infarction showed no signs of tumor recurrence.

DISCUSSION

Many authors have addressed the problems associated with carotid artery resection in patients with head and neck cancer.[2-9] Eight of these studies are presented in Table 3,[2-9] with the incidence of stroke and perioperative death and the combined stroke and death rates, for each. The postoperative incidence of stroke and death in our patients is clearly within the range of complication rates reported by other authors.

There are several possible explanations for the large variations among the data presented by different authors. First, some studies include only patients undergoing elective carotid resection, while others include emergent carotid ligation as well. Atkinson et al[9] reported an 8% perioperative death rate following 12 elective carotid resections, while the 58% perioperative death rate reported by Shumrick[6] may be attributed to the fact that 13 of his 19 cases were emergent. Similarly, Martinez et al[7] demonstrated a better survival rate in elective carotid artery resection than in emergent cases.

Gandhi and Oppenheimer[4] reported a 20% combined incidence of stroke and death following emergent carotid artery resection. They attribute their low complication rate to the fact that gradual thrombosis of the carotid artery allows development of collateral circulation, resulting in fewer postoperative neurologic complications. In addition, Moore et al[5] concluded that patients who develop neurologic complications and suffer perioperative death following carotid artery resection are most commonly those patients who develop shock.

The mean life expectancy in our patients following carotid artery resection of 9.6 months compares favorably with other studies. Hollmann and Timmel[10] examined patient survival following internal carotid artery resection in 30 head and neck cancer patients and reported a mean life expectancy of 4 months. The longest survivor they reported lived for 20 months, while our longest survivor lived 34 months, after which he was lost to follow-up.

Several methods have been described to predict the safety of carotid artery resection. These include intraoperative electroencephalography, carotid stump pressure monitoring, ocular plethysmography, somatosensory-evoked cortical potentials, and temporary balloon occlusion with xenon-enhanced computed tomography of cerebral blood flow. Intraoperative electroencephalography has the disadvantage of failing to predict delayed onset of stroke. In our series, four of five strokes were delayed more than 24 hours after surgery.

Ehrenfeld et al[11] concluded that a systolic stump pressure of greater than 70 mm Hg indicates adequacy of collateral circulation. They also noted that intermediate stump pressures of 55 to 68 mm Hg represent a genuine hazard and that pressures below 55 mm Hg result in an unacceptable stroke rate. Others, however, have shown that carotid stump pressure is an inaccurate predictor of subsequent neurologic compromise.[12]

Ocular plethysmography, as described by Martinez et al,[7] uses intraocular pressure to measure cerebral blood flow. This method allows one to predict accurately and reliably the adequacy of collateral flow to compensate for carotid artery resection. Atkinson et al[9] used somatosensory-evoked cortical potentials in conjunction with carotid stump pressure with good results. One of the most recent advances in this area is the use by de Vries et al[13] of temporary balloon occlusion with xenon-enhanced computed tomography of cerebral blood flow. This method seems promising, although further studies are necessary to obtain statistically significant data.

Carotid artery resection is a technically feasible operation with a reasonable perioperative complication rate, considering the severity of the insult to the patient. While this procedure may prolong the disease-free interval, it does not appear to increase patient survival, and the severity of resulting complications may shorten the lives of some patients. A reasonable assessment of the risks to the individual is necessary in each circumstance, and informed consent is mandatory. Patients must be advised of the considerable morbidity and mortality rates associated with this procedure. It is our hope that this study and the other studies reviewed will aid the head and neck surgeon in assessing the risks involved with carotid artery resection.

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The American Diopter and Decibel Society will hold its biennial meeting January 16-23, 1993, at the Westin Camino Real in Puerto Vallarta, Mexico. Abstracts are currently being accepted. For further information, contact Robin L. Wagner, American Diopter and Decibel Society, 3518 Fifth Avenue, Pittsburgh, PA 15213; fax (412) 647-8720, phone (412) 647-2227.

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COMPUTER APPLICATIONS IN OTOLARYNGOLOGY

COMPUTER RECOGNITION OF BRAIN STEM AUDITORY EVOKED POTENTIAL WAVE V BY A NEURAL NETWORK

DONALD T. FREEMAN, MS
PITTSBURGH, PENNSYLVANIA

A neural network simulator was used for the recognition of the presence and location of the peak of wave V of the brain stem auditory evoked potential (BAEP) test. Waveforms selected from BAEPs performed in the last 4 years at the University of Pittsburgh Presbyterian University Hospital were digitized and sampled, and the resulting amplitudes were normalized. A training set was composed of the waveforms resulting from the stimulation of 50 ears. The normalized amplitudes were used as the initial activation values for the networks. The desired outputs (the target locations for wave V) were represented in the output layer by setting the output element, which corresponded to the target location and its immediate neighbors, to high activation levels, and all the remaining output units to zero activity. Two network architectures, differing only in the hidden unit layer, with 40 and 16 hidden units, respectively, were trained by using standard back-propagation. Several trials from different starting points were performed for each architecture. The best network, found after 60 epochs (3,000 presentations), was able to correctly identify 17 of 20 cases (85%) from a set of test cases that were independent from the training set.

KEY WORDS — computer-assisted diagnosis, computer-assisted image processing, exemplar-based machine learning.

INTRODUCTION

Complex waveform recognition is generally considered to be a difficult task for machines. Analytic approaches to this problem have been described, and they work with reasonable accuracy.[1,2] These techniques, however, require substantial mathematical training, and the process is often time-consuming and labor-intensive.[3] Mathematic modeling also requires substantial knowledge of the particular details of the waveforms in order to determine how to apply the models and to determine detection criteria. Rule-based expert systems have also been used for the recognition of waveforms.[4] They require that a knowledge engineer work closely with a domain expert to extract the rules that the expert uses to perform the recognition. If the rules are ad hoc or if it is difficult for experts to articulate the rules they use, then rule-based expert systems are cumbersome to implement.

This paper describes the use of neural networks to recognize the location of peak V from the waveform recording of brain stem auditory evoked potential (BAEP) tests. General discussions of connectionist networks can be found elsewhere.[5] The main features of neural networks that are relevant for our purposes revolve around their ease of use as compared to other modeling techniques. Neural networks provide several advantages over modeling with differential equations or rule-based systems. First, there is no knowledge engineering phase. The network is trained automatically by using a series of examples, along with the "right answer" to each example. Second, the resulting network typically has significant predictive power when novel examples are presented. So, neural network technology allows expert performance to be mimicked without requiring that expert knowledge be codified in a traditional fashion. In addition, neural networks, when used to perform signal analysis, require vastly less restrictive assumptions about the structure of the input signal than do analytic techniques.[6] Neural nets have not yet been widely applied to problems of this sort.[7] Nevertheless, it seems that interest is growing in using computers, especially neural networks, to solve advanced problems in medical decision-making.[8-10]

NEURAL NETWORKS

Neural network modeling, also called *connectionism*, uses ideas from neuroscience and computer science to develop machines that perform complex recognition tasks. Neural networks are an alternative to classic computing techniques and traditional artificial intelligence techniques. They are particularly good at learning by example, at fault-tolerant (error-tolerant) computing, and at pattern recognition.

Artificial neural networks were inspired by characteristics of living neural systems. Biologic neurons have multiple input paths (dendrites), which transmit possibly multiple weak input signals to the cell body, in which these multiple contributions are "evaluated" in a way that changes the probability that the cell will

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From the Intelligent Systems Program and School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania. This research was supported by National Library of Medicine Training Grant T15 LM-07059.

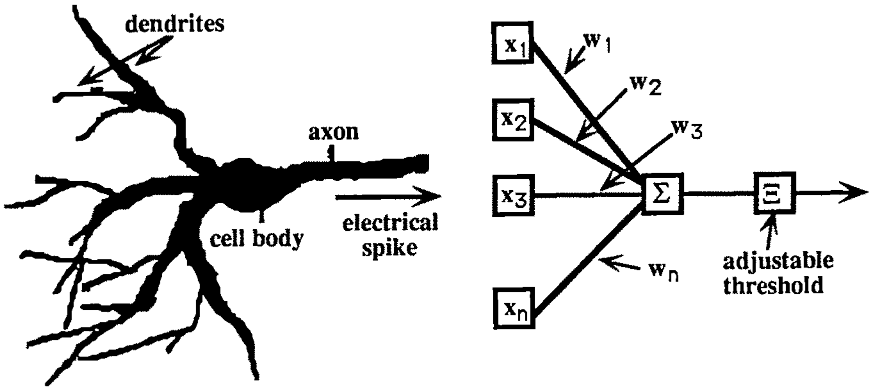

Fig 1. Schematic diagram of processing element, natural and artificial. xi—input stimulus, wi—weight, Σ—linear sum.

deliver an action potential along its axon. The axon may stimulate or inhibit the dendrites of one or many other cells, including its own.

At the center of the computational model of a neuron is the *processing element*, or *unit*. The basic structure of a processing element includes several parts, as diagrammed in Fig 1. A processing element may have one or many input paths, usually from other processing units but sometimes from an external source. Each input, called a stimulus, is multiplied by the weight associated with its input path, shown as w1, w2,...,wn. The processing element adds these adjusted stimuli together to generate the weighted sum of the stimuli and then uses a nonlinear transfer function, T, to compute its output, also called the unit's *activity*. The activity is passed to the output path, which connects to one or more other elements. This output value may become the stimulus value for other processing elements to which the unit is connected.

Different transfer functions may be employed. The transfer function may yield an all-or-none response, or it may be continuous, resulting in more activation as the stimuli to the processing element increase in strength. The transfer function for input units is the identity function, passing activation to the output path without changing it. The input paths are analogous to dendrites in biologic systems. The weights on the input paths correspond to the synaptic connection strength. The summation and transfer functions can be taken to reflect processing that happens at the axon hillock, and the output path is analogous to the axon itself.

Typically, processing elements are arranged into groups, or *layers*, that may connect in various ways. The three-layer network shown in Fig 2 is the typical organization for neural networks that use the back-propagation of error learning paradigm, which will be discussed briefly below. An *input* layer accepts the stimuli from the "outside world" directly and performs no processing, each unit passing its input directly to the output path. The *output* paths from the input layer connect to a group of units that are between the input and output layers; they are called *hidden* units. In a three-layer network, these hidden units have output paths that connect to the output layer. Hinton[11] showed that hidden units sometimes respond to specific features in the input pattern; hence, the hidden units are sometimes considered to be *feature detectors*. However, a precise understanding of the behavior of the hidden unit layer remains an active research topic.[12] Each unit of the output layer calculates the linear sum of the inputs from the hidden layer to the output unit and passes the result through the transfer function. The resulting activity on the unit is one of the outputs of the net. The activities of these units are read as the output of the network and often represent different pattern classifications. In a *fully connected* network, each element is connected to every element in the adjacent layers.

Processing of inputs by a neural net involves presenting stimuli to the input nodes. These stimuli are typically real numbers between −1 and 1. The value of each of these numbers corresponds to some feature of the inputs, and the input unit is said to represent that feature. For example, each input unit of a net could represent the amplitude of a wave at a particular time where 0 corresponded to no amplitude and 1 corresponded to the maximum amplitude. Ten input units could correspond to 10 samples of the amplitude of the wave at the 10 time points represented by each of the units.

The input values are sent to the input units' output path, which connects to one or more of the units in the hidden layer. The activity of each of these hidden units is determined by first multiplying each of its input path stimuli (from the outputs of the previous layer) by the input path weight and adding them together to form the linear sum. This sum is passed to a transfer function and the result of that function becomes the activity of the unit. This activity is sent to the output path of the unit. The units in the output layer perform the same calculations, and the activi-

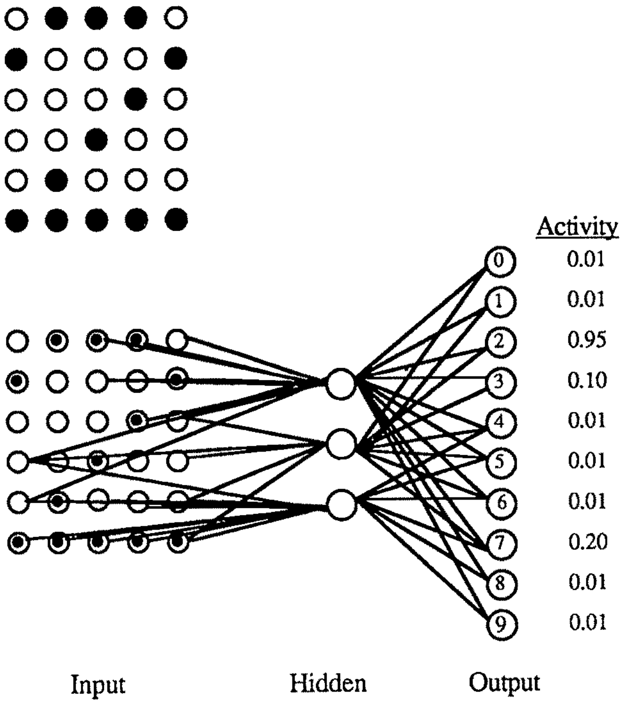

Fig 2. Recognition of numeral 2 by neural network. Not all connections are shown. Activity is in milliseconds.

ties of the output units are the outputs of the net.

One key to the proper performance of a network is the setting of appropriate weights. Once finalized, the weights remain constant and determine the activities on the hidden and output units from the activities of the input units. An important feature of these systems is that they can automatically learn the appropriate connection strengths necessary to produce the "correct" output by applying a learning rule.

Neural networks can be made to adjust the weights, or learn, if they are given an input and the output that is expected from the input. The set of examples along with the "right answers" is called the training set. One popular training procedure, the back-propagation of error method, proceeds in several steps. First, the input is presented to the input nodes. The hidden layer activities are calculated and then the output layer activities are calculated. Next, the actual output activities are compared to the desired activities. When a unit's activity differs from the activity that was needed to produce the correct output (the desired response), the degree to which the network made a mistake is called the error. For example, if an output node response was 0.3 but the correct response was 1.0, then the error was 0.7. The weights on the input path to that unit are adjusted so that the activity on that unit will be closer to the desired activity for that example, and they are adjusted in proportion to the amount of the error. While it is not difficult to calculate an error for the output nodes because the activity and the desired answer are known at the output layer, no such "desired answer" is known for the hidden unit layer. An "effective" desired answer is calculated for the hidden unit layer and the process is repeated for the hidden units, hence the name *back-propagation* for this phase of learning.

Many iterations of the process may be necessary before the weights are set to optimum values during the learning phase by the back-propagation algorithm. The learning process is repeated after each case has been presented. After many case presentations the network becomes trained. This is called supervised learning, because the "rewards" and "punishments" are provided by a knowledgeable teaching program (the learning part of the network simulator) with the answers in hand. After training, the net may be applied to test cases in which the answers are not known.

One useful feature of neural nets is that they do more than simply "memorize" the cases in the training set. If they only memorized, then the net could only provide correct answers when the inputs to the net were identical to the inputs in one of the training cases. Instead, these networks are said to generalize. Inputs that differ from the training examples are often handled well. After appropriate training, the nets are often robust to noisy and missing data in the input. Furthermore, some "gestalt" is developed from the training set that often allows inputs substantially different from the training example inputs to be managed well.

Neural Networks Versus Traditional Computing. Traditional computers execute instructions one at a time, in sequence, until a final result is achieved. In contrast, each of the processing units of a neural network can operate in parallel with all the other units of the network. (Note that a standard computer can be used to *simulate* such a network so that no special hardware is required.) The power of neural networks comes from the interaction of a large number of simple processing elements, each sending signals to other units. This results in a very different approach to problem-solving when neural networks are employed rather than traditional programs or artificial intelligence approaches.

Consider the example in Fig 2. Suppose we wish to recognize the number 2 represented as the arrangement of pixels, as is the case for mechanical displays. We may use either traditional rule-based expert systems or a neural network to perform the recognition task.

Rule-based expert systems represent the symbolic knowledge that they use to solve problems as a set of

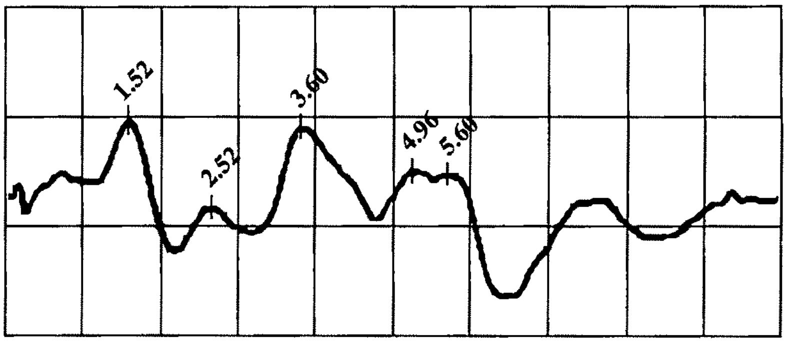

Fig 3. Brain stem auditory evoked potential chart showing graph of averaged ipsilateral potentials with waves I to V identified. Points shown are milliseconds.

IF x THEN y rules. The rule to recognize the number 2 might be

IF horizontals = 2 AND diagonals = 3

THEN conclude numeral = "2"

Since rule-based expert systems only accept symbolic information as their inputs, a separate program must be written to extract the important *features* of this task—the horizontal, vertical, and diagonal lines from the illuminated dots of our display example. This program itself might require substantial artificial and engineering intelligence. The output of such a program would be the symbolic information used as inputs to the rule-based expert system recognition system, eg,

(line number = 1 : direction = horizontal : length = 3)

Construction of an artificial neural network takes a different approach. Neural networks are not programmed; they learn by example. Here we might imagine that each of the elements of the numeral display was hooked up to an artificial neuron that fired when that display element was illuminated. More precisely, each of the input nodes of the network would *represent* the state of one of the dots on the display. When a display dot is off, the network node representing it would receive an input value of 0. When a display element is on, the network node representing it would receive an input value of 1. In this example, input nodes are set to 0 or 1, but in many neural networks the input values take on any real value between two limits, often 0 and 1.

As shown in Fig 2, input nodes (30 of them) are activated or not activated, depending on the state of the display element they represent. All of the input nodes are connected to each of three hidden units. These hidden units are connected to 10 output units, each of which represents the presence of a digit, as labeled.

To recognize a digit in a neural network, the activation of the input units is passed to the hidden units on the basis of the value of the weight connecting the input to the hidden unit. For example, if a 0.7 weight connects an input unit whose activity is 1.0 to a hidden unit, then the contribution of that input unit to the hidden unit is 0.7. Each hidden unit sums the many contributions to it from the input nodes and sends this value through the transfer function, and the resulting value is the output or activity of the hidden unit. The whole process is repeated between the hidden layer and the output layer.

The result of this process is shown in the activity of the output nodes. The node representing the numeral 2 has a high activation, at 0.95. The node representing the numeral 7 (a numeral frequently confused with 2) has the next highest activation, at 0.2 — well below the activation for the numeral 2. All the other activities are negligible. The key to the success of this computation is that the weights have the correct values. The weights can be learned by presenting the input patterns of a numeral as well as the desired answer (1.0 on the node representing 2, and 0.0 on all the other nodes) during the learning phase.

This example illustrates some of the differences between traditional techniques and neural networks. Rule-based expert system techniques require that rules (which may not even exist) be extracted from an expert, with the advantage that by following the rules used for a conclusion we can understand how the expert system reached a conclusion. Also, small differences in the way information is represented — such as different ways of writing the number 2 — can result in dramatic differences in performance. Should the line recognition program yield results even slightly different from those that are expected, recognition becomes impossible. This is *brittle* behavior of the program and is unsatisfactory for domains in which input data are noisy.

Neural networks learn associations between input and output patterns automatically, storing these associations as weights. However, it may be difficult to explain their behavior, since multiple contributions of information from weak sources ultimately combine to provide a final answer. A neural network can generalize on the task for which it is trained, enabling the network to provide the correct answer when it is

TABLE 1. COMPOSITION OF INPUT DATA

		Abnormal Ears			
Cases	*Normal Ears*	*Prolonged V*	*Absent V*	*Total*	*Total Ears*
Training	39	8	3	11	50
Testing	18	0	2	2	20

presented with an example that is only analogous to the training examples. The networks can be trained to be sensitive to small differences in the inputs that matter but insensitive to noise. This *robust* behavior is required for successful interpretation of noisy data.

It is important to remember that artificial neural networks should not be construed as a "valid" model of biologic neurons, although they have been used to investigate biologic neural processes. The characteristics of artificial neural networks are explained by the mathematic models that define the processing elements. Although we use broad behavioral terms such as learn, generalize, and adapt, neural network behavior is quantifiable, with a firm mathematic foundation in statistical thermodynamics.

BRAIN STEM AUDITORY EVOKED POTENTIAL

Evoked potentials are electrical signals from the brain that occur in response to transient auditory, somatosensory, or visual stimuli such as a click, pinprick, or flash of light. The signals, recorded from electrodes placed on a subject's scalp, are a measure of the electrical activity in the subject's brain both from response to the stimulus and from the spontaneous electroencephalographic activity of the brain. One way of discerning the response to the stimulus from the background electroencephalographic noise is to average the individual responses from many identical stimuli. When "cortical noise" has been removed in this way, evoked potentials can be an important noninvasive measure of central nervous system function. Although BAEPs are used for many reasons,[13] attention has recently focused on continuous automated monitoring of the BAEP intraoperatively as well as postoperatively for evaluation of central nervous system function.[14]

A typical auditory brain stem response (ABR) waveform has seven important peaks, but often includes other peaks resulting from the noise that remains after averaging (Fig 3). The time of arrival of the peaks (the peak latencies) and the amplitudes of the peaks are used to characterize the response. It is of interest that the times of arrival of a wave on the ipsilateral and contralateral sides may be slightly different. This effect becomes more exaggerated the more distant the correlated peaks are from the origin.[15]

There are several issues in the interpretation of the waveform. First, it must be clear that some neural response to the auditory stimulus is represented in the waveform. If a response is present, the peaks that correspond to normal and abnormal responses must be distinguished from noise that remains in the signal even after averaging. Wave IV and wave V occasionally fuse, forming a wave IV/V complex and confounding this process. In these cases we say that wave V is absent. Finally, the latencies and possibly the amplitudes of the identified peaks are to be measured and a diagnostic explanation for them is developed.

Neural networks have the potential to learn the associations needed to make these decisions, automatically interpreting the ABR recording. Such an application would be similar to the rule-based expert system that is currently used to interpret electrocardiograms. Experience with the latter may ameliorate concern over replacement; automated interpretations do not threaten to replace cardiologists. It is possible that such systems improve human performance by putting personnel in a "critiquing" position rather than having to develop an interpretation for the first time.

METHODS

DATA

Plots of BAEP tests were obtained from the evoked potential files from the last 4 years at the University of Pittsburgh Presbyterian University Hospital. In the protocol used there, a series of 2,000 clicks is delivered and the results from each click — electrode activity over 10 milliseconds — are averaged into a single graph. We refer to the results from the stimulation of one ear with the clicks as " one ear of data."

A preliminary group of *training cases* consisting of 13 patients or 26 ears was selected by traversing the files alphabetically from the beginning of the alphabet. This group was subsequently enlarged to 25 patients or 50 ears (39 normal and 11 abnormal). Most BAEP tests showed no abnormalities; only 1 of the first 40 ears was abnormal. In order to create a training set with an adequate number of abnormal cases, we included 10 additional ears with abnormal ABR recordings. For *test cases*, 10 patients (20 ears) were randomly selected. No cases were common to both sets. Table 1 summarizes the input data. The experiments were performed on the Apple Macintosh-II computer using Neural Works Professional II Version 3.5 (NeuralWare, Inc, Pittsburgh, Pa), BitPad Plus (Summagraphics Corp, Fairfield, Conn), and DigiGraf (Edmonton, Canada). The ipsilateral and contralateral wave recordings were transformed to

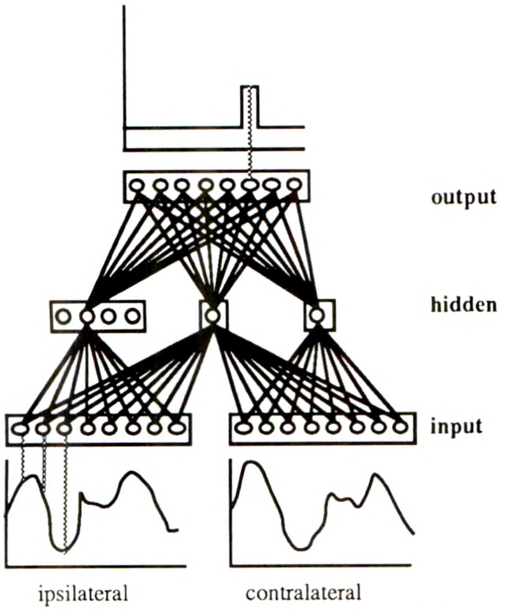

Fig 4. Diagram of architecture 1 with representation of input and output data shown.

machine-readable format by manual tracing with the BitPad Plus digitizer. The approximately 400 points that resulted from the digitization of each ear were graphed and compared to the original tracings. If the tracings did not match, then the transcription was performed again. In addition, the originally recorded latency values for peak V were corrected for any distortion in the digitizing process. The distortion was judged by a neurologist to be minimal.

A program was written to process the digital waveforms, creating an output file readable by the neural network simulator. The program discarded the first and last milliseconds of the recordings. The remaining points were sampled at 0.1-millisecond intervals by using linear interpolation to estimate an amplitude if a point had not been recorded within 0.01 millisecond of the desired time. These points were then normalized to the range <–1,1>. The resulting 80 points for the ipsilateral wave and 80 points for the contralateral wave (a total of 160 points) were used as the initial activations for the input layer of processing elements.

ARCHITECTURES

Each of the two network architectures had 160 input nodes. Each node represented the amplitude of the wave at each sample time (1.0 to 8.9 milliseconds, every 0.1 milliseconds). Each architecture also had 80 output nodes with a similar temporal interpretation (Fig 4). Architecture 1 had 30 hidden units connected only to the iplilateral input units, 5 hidden units connected only to the contralateral input units, and 5 hidden units connected to all the input units. The hidden units for both architectures were fully connected to the output units. Architecture 2 had 16 ipsilateral hidden units, 3 contralateral, and 3 connected to both. Both architectures used the sigmoid transfer function at both the hidden and output layers. All units were attached to a bias unit.

The distribution of the hidden units was chosen with the knowledge that human experts usually use information from the ipsilateral side and refer to the contralateral side only when features in the ipsilateral side are too obscure to resolve. The selection of the number of hidden units in neural network models remains an art. In order to determine whether the size of the hidden unit layer could be changed, we performed similar experiments using architecture 1 and architecture 2.

TRAINING

For training, target values for the output layer were all 0.0, except for the output nodes representing the time of arrival for wave V (reported on the BAEP chart), and one node on each side of it. The peak node target was 0.95, and the two adjacent nodes had targets of 0.90. For cases in which wave V was absent, the target for all the output nodes was 0.0.

A neural network simulator (Neural Works Professional II) and an Apple Macintosh-II computer were used to construct the networks and run the simulations. The back-propagation learning algorithm was used to train the networks. The random number generator was initialized with random number seeds taken from a random number table. Then network weights were initialized to random values between –0.2 and 0.2 and the training was begun. Since our random number generator is deterministic — given the random number seed — these trials are replicable.

Each of the 50 ears of data in the training set was presented in a random fashion (randomize, shuffle, and deal technique). Network weights were saved at various stages of learning, usually after every 1,000 presentations (20 epochs), until the cumulative root mean squared error for an epoch fell below 0.01. The contribution of each training example to the total error was examined to determine whether a few examples were the source of most of the error. If so, training was continued until these examples had been learned to an error level comparable to that of the rest of the cases. After training, the 20 ears in the test set were presented to each of the saved networks, and the output nodes of the net were examined for each test case.

ANALYSIS OF RESULTS

A threshold method was used to analyze the data. For each of the test cases the actual location of the

TABLE 2. RESULTS FROM PRESENTATION OF 20 TEST CASES TO TWO NETWORKS

		Successful ID of V			*Unsuccessful ID of V*			
Trial	*Epochs*	*TP*	*TN*	*TT*	*FP*	*FN+*	*FN−*	*TF*
1	60	16	1	17	1	1	1	3
2	60	15	1	16	1	2	1	4
3	100	14	0	14	2	2	2	6
4	500	15	0	15	2	2	1	5
5	20	14	0	14	2	3	1	6
6	20	15	0	15	2	2	1	5
7	40	15	0	15	2	1	2	5
8	100	15	0	15	2	1	2	5
9	1,000	16	0	16	2	2	0	4

Trials 1 through 7 are with 40–hidden unit network. Trials 8 and 9 are with 16–hidden unit network.

ID—identification, V—wave V, TP—true positive, TN—true negative, TT—total true, FP—false positive, FN+—false negative with activation above threshold, FN−— false negative with activation below threshold, TF — total false.

maximum-value output unit was compared to the expected location of the maximum-value output unit. For network results to be classified as a correct identification in the wave V-present case (true positive), we require that the maximum-value output unit have an activation that is over an activity threshold (0.50) and that the unit be within a distance threshold (0.2 millisecond) of the expected location of wave V. For a true negative identification of wave V — a correct identification of wave V's being absent—we require that all the output activities be below the activity threshold and that the case have no wave V to find. The network makes a false-positive prediction of the location of wave V if some activity is above the activity threshold for a case that has no wave V. Finally, there are two ways for the network to make a false-negative identification of wave V. In both instances, wave V must be present in the case. In one instance, some output node has activity above the activity threshold, but it is outside the distance threshold. This corresponds to the identification of a wave V, but in the wrong place. In the other instance, no node attains activity over the activity threshold, corresponding to a failure to find a wave V when one exists.

EXPERIMENTS

Two experiments were performed. The first used architecture 1, while the second used architecture 2, each on the same data set. Each of the network architectures was trained from different random starting positions. For each trial (one training from one starting position), the network weights were randomized and training was performed as described above. The networks were sampled as learning progressed.

In experiment 1, seven trials determined how well architecture 1 could identify wave V and provided baseline results for the remaining experiment. Experiment 2 determined whether fewer hidden units could be used.

RESULTS

Results from the best network found for each of the experiments are shown in Table 2. Examining the results from the larger architecture (top of Table 2), the best network we found (trial 1) correctly identified wave V in 16 of the 18 wave V–present cases and in 1 of the wave V–absent cases for a total correct identification in 17 of the 20 test cases (85%). The incorrect identifications of wave V represent all the possible ways for the network to fail, composed of one false positive and two false negatives. In the false-positive case, wave V was absent, but the activation of one unit was 0.02 over the activity threshold of 0.5, indicating that the network predicted a location for wave V. Both of the possibilities for a false negative — an identification of the wave outside of the distance window and failure to identify a wave V at all — were found. In one of the false-negative identifications, wave V was identified just outside the distance threshold (maximum activity of 0.65 at 5.5 instead of 5.2 milliseconds). In the other false-negative case, no output node attained an activation over the activity threshold (maximum activity of 0.25 at 5.7 milliseconds).

The best smaller-architecture net correctly identified the location of wave V in 16 of the 18 wave V–present cases and in none of the wave V–absent cases, for a total correct identification in 16 of the 20 test cases (80%). Two of the remaining cases were false positives, with wave V being identified when it was actually absent. In both of the false-negative cases, the network predicted the existence of a wave V just outside the distance threshold (rather than failing to predict its existence at all).

DISCUSSION

The 3 cases that were incorrectly identified in the best large network were examined closely. It is not evident from inspection why the net failed to identify the peaks or why it identified peaks where there were none to identify. Where peaks are present, they are not unusually located or surrounded by noise. Their shape seems similar to that of the cases that were identified correctly. We believe that more training examples that are "similar" to these 3 test cases, as well as examples with greater variety, will improve recognition of these cases. This improvement comes not from better generalization, but rather from a reduced requirement for generalization. If the net is trained with cases that are increasingly similar to the cases that will be used to test it, then recognition of the test cases becomes easier at any given level of generalization. We have informally observed that when the number of training cases was increased from 13 to 25, the overall accuracy of the nets' predictions went from 50% to 85%, clearly improving the performance. Currently, it is not possible to assess in advance for any neural network what the final accuracy level attainable will be.

It is notable that in no case did the net select the wrong peak from a normal waveform, in spite of the variability of our data, which increased the probability of this kind of misidentification. Wave V usually appears within the range of 5.2 to 5.9 milliseconds.[15] Our data were more variable, with the training cases ranging from 4.8 to 6.6 milliseconds and the test cases ranging from 5.0 to 5.8 milliseconds.

The performance of the network with 16 hidden units was comparable to that of the 40–hidden unit architecture. Since the hidden unit layer effectively re-represents the inputs in an unknown feature space, one interpretation of this result is that few features are needed for wave V recognition. Another interpretation is that significant data compression or information loss is possible while retaining good recognition of wave V. Indeed, if information about the location of the other waves is not needed for the identification of each wave, then it is probable that a fraction of the input data are being used for recognition. Informally, we have observed that only the weights connected to input units in the range of 4.5 to 6.5 milliseconds are dramatically changed in learning. This important result indicates that when we extend the network to locate the positions of other waves, there will not be a combinatorial explosion of the information required by the net. Instead, a group of hidden units connected only to a small portion of the input layer might act as a "local expert" for the identification of a peak. Several such groups could be used to identify each peak.

CONCLUSIONS

Automated waveform recognition is considered to be a difficult task for machines, and an especially difficult task for neural networks. Our results offer some encouragement that neural networks may be applied to perform waveform recognition and that the technique will be extensible as problem complexity increases.

Still, the accuracy of the networks we have discussed is not high enough for clinical use. Several extensions have been attempted and others considered, including 1) increasing the sampling rate to decrease the granularity of the input data, 2) increasing the training set size, 3) using a different representation of the output for wave V–absent cases, 4) using a different representation of the input, such as the derivative of the amplitudes, and 5) using architectures that allow hybrids of these ideas.

Finally, since many other tests in medicine as well as other fields require the interpretation of graphical data, it is tempting to consider extending this method to other domains. One distinguishing feature of the BAEP is that there is no difficulty with the time registration of the data; we always know where to start looking for the wave. This is in contrast to an electrocardiogram, for example, which may require substantial effort just to identify the beginning of a QRS complex. Our results indicate that neural networks can be used for the interpretation of graphs in which the time registration of data is not an issue. Medical tests for which this technique would be appropriate include other evoked potentials, spectrometry, and gel electrophoresis.

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THIRD INTERNATIONAL CONFERENCE ON PEDIATRIC OTORHINOLARYNGOLOGY

The Third International Conference on Pediatric Otorhinolaryngology of the "European Pediatric Otolaryngology Working Group" will be held in Jerusalem, November 7-12, 1993. For more information, contact Prof Jacob Sadé, 14 Hagefen St, Ramat-Hasharon 47254, Israel; telephone 972-3-5494275; fax 972-3-655674.

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IMAGING CASE STUDY OF THE MONTH

INTRAPAROTID HEMATOMA

ARTHUR M. LAURETANO, MD
MICHAEL J. CUNNINGHAM, MD ALFRED L. WEBER, MD
BOSTON, MASSACHUSETTS

With the possible exception of the often clinically apparent hemangioma-lymphangioma, the presence of a unilateral parotid mass in a child is of diagnostic concern. This is particularly true of a child in whom a firm mass arises within a short period of time without associated infectious or inflammatory symptoms.[1]

CASE REPORT

A 6-year-old, otherwise healthy boy presented with a progressively enlarging, painless, left lateral facial mass of 2 weeks' duration. He had no associated otologic or systemic symptoms. His history was noteworthy only for an incidental episode of localized blunt trauma to the left lateral facial region several days previously.

Physical examination revealed a firm left parotid mass, 5 cm in diameter, without associated erythema or ecchymosis (Fig 1). Findings on otologic examination were unremarkable. Oropharyngeal examination revealed a normal Stensen's duct orifice and no lateral buccal or pharyngeal wall asymmetry. No cervical lymphadenopathy or additional masses were appreciable on neck palpation. Facial nerve function was normal bilaterally. His right parotid and general examinations yielded normal findings. Laboratory analysis revealed normal complete blood count, prothrombin time, partial thromboplastin time, and bleeding time.

Computed tomography performed without contrast material revealed a left intraparotid mass containing both high- and low-density components (Fig 2). These components layered out differently on axial and coronal scans and were consistent with fluid-fluid levels. No chronic inflammatory glandular changes were apparent, and no associated lymphadenopathy was noted. The right parotid gland appeared normal. The initial radiologic interpretation reported these findings to be consistent with a left parotid lymphangioma.

Diagnostic operative evaluation under general anesthesia was performed via 20-gauge fine-needle aspiration biopsy. The mass completely disappeared following aspiration of 12 mL of coagulated blood. Aerobic and anaerobic cultures proved negative, and cytology revealed solely blood elements.

A slight reaccumulation of soft tissue fullness was noted on removal of a pressure dressing on the first postoperative day. This resolved spontaneously, and follow-up examination 3 weeks later showed no evidence of recurrence. This child remains well 1½ years postaspiration.

DISCUSSION

The differential diagnosis of a unilateral, solid parotid mass in childhood includes benign follicular hyperplasia of intraparotid and paraparotid lymph nodes, inflammatory processes such as cat-scratch disease and atypical mycobacterial infection, and neoplasms.[1-3] Solid neoplasms reported in the pediatric population include the benign pleomorphic adenoma and a variety of comparatively rare primary salivary gland malignancies.[1-3] The rapid enlargement and firm physical characteristics of this child's mass on presentation prompted suspicion of a neoplasm, necessitating an expedient and thor-

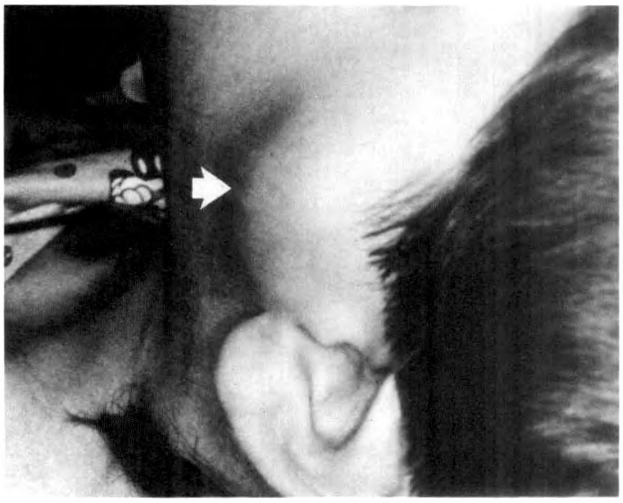

Fig 1. Six-year-old boy with left parotid region mass 5 cm in diameter (arrow).

From the Departments of Otolaryngology (Lauretano, Cunningham) and Radiology (Weber), Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, Massachusetts.

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REPRINTS — Michael J. Cunningham, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

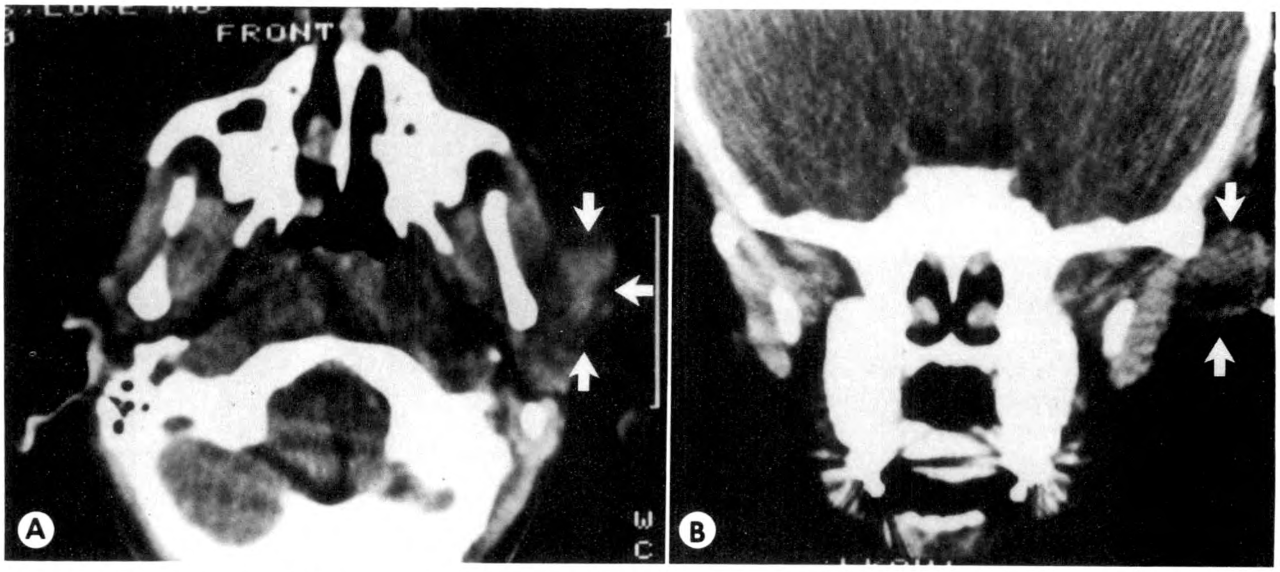

Fig 2. Computed tomographic images reveal left intraparotid mass (arrows) containing both high- and low-density components that layer out differently on A) axial and B) coronal scanning. Remaining parotid parenchyma is normal.

ough evaluation.

A variety of radiographic techniques — plain films, sialography, ultrasound, radionuclide scans, computed tomography (CT), and magnetic resonance imaging (MRI) — have been employed in the evaluation of parotid gland disorders.

The use of plain radiographs is principally limited to the detection of the approximately 20% of parotid calculi that are radiopaque.[4] Contrast sialography enhances this yield by demonstrating obstructive radiolucent stones and inherent parotid duct abnormalities such as strictures, dilatations, and sialectasia.[4,5] The technical performance of contrast sialography can be quite difficult in young children.

Ultrasonography provides adequate visualization of parotid morphology and can often distinguish intraparotid from extraparotid lesions.[6] The absence of radiation exposure and the lack of reliance on patient cooperation make this radiographic technique quite applicable to the pediatric population. Its greatest potential value is distinguishing between cystic and solid masses; it cannot, however, differentiate diagnostically among solid or mixed density parotid lesions.[6]

Radionuclide scans have proven useful in the evaluation of certain specific parotid neoplasms and glandular disorders; the limited spatial resolution of such scans makes them generally inferior to the imaging capabilities of CT and MRI.[4]

Computed tomography is an excellent modality for parotid gland imaging.[4,5,7-10] It typically allows differentiation of extrinsic from intrinsic parotid lesions and defines the location of such lesions relative to surrounding anatomic landmarks.[4,9] When performed with the concomitant administration of intravenous and/or sialographic contrast, a distinction between benign versus malignant disease can occasionally be made.[4,8,9] Computed tomography scanning proved particularly useful in this child. The axial and coronal CT images revealed the mass to be clearly intraparotid, of mixed density with a suggestion of fluid-fluid levels, and without associated inflammatory changes within the remaining parotid tissues. These radiographic findings prompted the performance of a diagnostic and ultimately therapeutic fine-needle aspiration procedure.

Magnetic resonance imaging has recently emerged as the superior method of radiographic parotid assessment.[11,12] It provides excellent soft tissue characterization and discrimination and therefore better definition of normal and diseased tissue, especially in evaluation of cysts and tumors. Magnetic resonance imaging, however, is difficult in children because of the confining nature of the imaging apparatus. General anesthesia may be necessary in such cases. This potential need, in light of the CT scan findings, led to the decision not to perform MRI in this child.

Our review of the literature revealed no previously reported cases of intraparotid hematoma occurring spontaneously or after blunt trauma in either the adult or pediatric populations. Parotid hematoma has been listed as one of the complications arising from parotidectomy and fine-needle aspiration.[13-16] Even within this context, hematoma formation is still a rare occurrence. In one series of 336 parotidectomies, hematoma occurred in less than 0.03% of cases.[12] Similarly, although case reports of the occurrence of hemorrhage after fine-needle biopsy do exist,[14] several extensive reviews of the use of fine-needle aspiration and biopsy technique in the diagnosis of parotid lesions do not document hematoma as an encountered complication.[14,16,17]

CONCLUSION

This case represents the interesting finding of a rapidly enlarging parotid mass occurring after incidental local trauma. The cystic components of the mass were not clinically appreciable, and its firm appearance on palpation heightened diagnostic concern. Computed tomography established the mixed density composition of the mass, and needle aspiration proved to be both diagnostic and therapeutic.

This entity of intraparotid hematoma has previously been described as a complication of parotid surgery and a potential complication of needle biopsy. It has not been reported as arising in association with blunt parotid trauma.

Certainly, in the pediatric population, a rapidly expanding parotid mass warrants definitive etiologic investigation. We recommend that the entity of intraparotid hematoma be considered in the differential diagnosis of parotid masses, especially if there is a history of recent localized trauma, no matter how incidental.

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PATHOLOGY CONSULTATION

AMYLOIDOSIS IN THE UPPER AERODIGESTIVE TRACTS

A. KEVIN RAYMOND, MD
NOUR SNEIGE, MD
JOHN G. BATSAKIS, MD
HOUSTON, TEXAS

The upper aerodigestive tracts, particularly the larynx, are not uncommon repositories for amyloid. In most instances amyloidosis of the larynx is localized and is not associated with or followed by systemic disease. Oral and nasopharyngeal amyloidoses, on the other hand, are very often manifestations of systemic predisposing disorders. Laryngeal amyloidosis is treated, when indicated, by surgical removal, often repeated because of persistence or multifocal deposits.

Amyloidosis is not a single clinicopathologic entity but rather a grouping of disorders, all of which are characterized by deposition of an acellular proteinaceous material (amyloid) in tissues.[1-3] It most often occurs as a primary disease or in association with plasma cell dyscrasias or inflammatory diseases. Less often, it can be inherited or be a concomitant of aging. In primary, secondary, and some of the familial forms of amyloidosis, there is a systemic involvement of tissues. Localized forms also occur but the amyloid in all types has similar morphologic, structural, and staining properties despite involvement of fundamentally different protein components.[4,5]

Glenner[2] has shown that the unifying definition of amyloid deposits is that they are aggregates of proteinaceous twisted β-pleated sheet fibrils of considerable chemical diversity. In addition to the fibrils, all amyloid deposits contain amyloid P component, a nonfibrillar glycoprotein that is identical to and derived from serum amyloid P, a normal circulating protein. Amino acid analyses have shown the amyloid protein contains all of the common amino acids. There is a preponderance of aspartic acid and glutamic acid residues.[6] These comprise as much as 20% of the total amino acid content, thereby creating the highly polyanionic environment that is typical of amyloid fibrils.[6]

As seen with the light microscope, amyloid is a homogeneous, acellular, eosinophilic (with hematoxylin and eosin stains), and extracellular material. It stains metachromatically with crystal violet and characteristically manifests a Congo red staining of its fibrils. The latter, examined under polarized light, have an apple-green birefringence. Exposure of the Congo red to potassium permanganate and dilute sulfuric acid may be used to partly subclassify amyloid. Electron optic examination indicates amyloid is a fibrous protein with rigid and nonbranching fibrils of 7.5 to 10 nm in width. The β-pleated sheet configuration of the fibrils is seen with x-ray diffraction and spectroscopic examination.[1-5]

Current classifications of the amyloidoses are based on the biochemical nature of the protein subunits.[1,7] Immunoglobulin light chain–derived amyloid or type AL amyloid consists of κ or λ monoclonal light chains. It is this type that is associated with primary systemic amyloidosis, myeloma-associated amyloid, and most localized forms of amyloid. Amyloid A (type AA) protein is found in secondary amyloidosis and familial Mediterranean fever. Transthyretin (prealbumin) is the protein in the fibrils of familial and senile cardiac amyloidosis. Amyloid associated with chronic dialysis contains β2-microglobulin.

It has been established that in systemic amyloidosis, chronic inflammatory diseases predispose to deposition of AA amyloid, whereas plasma cell dyscrasias predispose to AL amyloid.[1-3,5-7] When a localized amyloid is associated with a chronic inflammatory reaction, the amyloid is usually AL.[1] In some forms of localized amyloidosis, the amyloid is associated with a hormone, prealbumin, or keratin.

AMYLOIDOSIS IN AERODIGESTIVE TRACTS

Amyloid deposition in the head and neck can occur in the absence of any systemic involvement or associated diseases, or be part of a systemic amyloidosis with or without plasma cell dyscrasias. Localized amyloid has presented in major and minor salivary glands, oral cavity and pharynx, nasopharynx, sinonasal cavities, larynx, trachea, bronchi and lungs,

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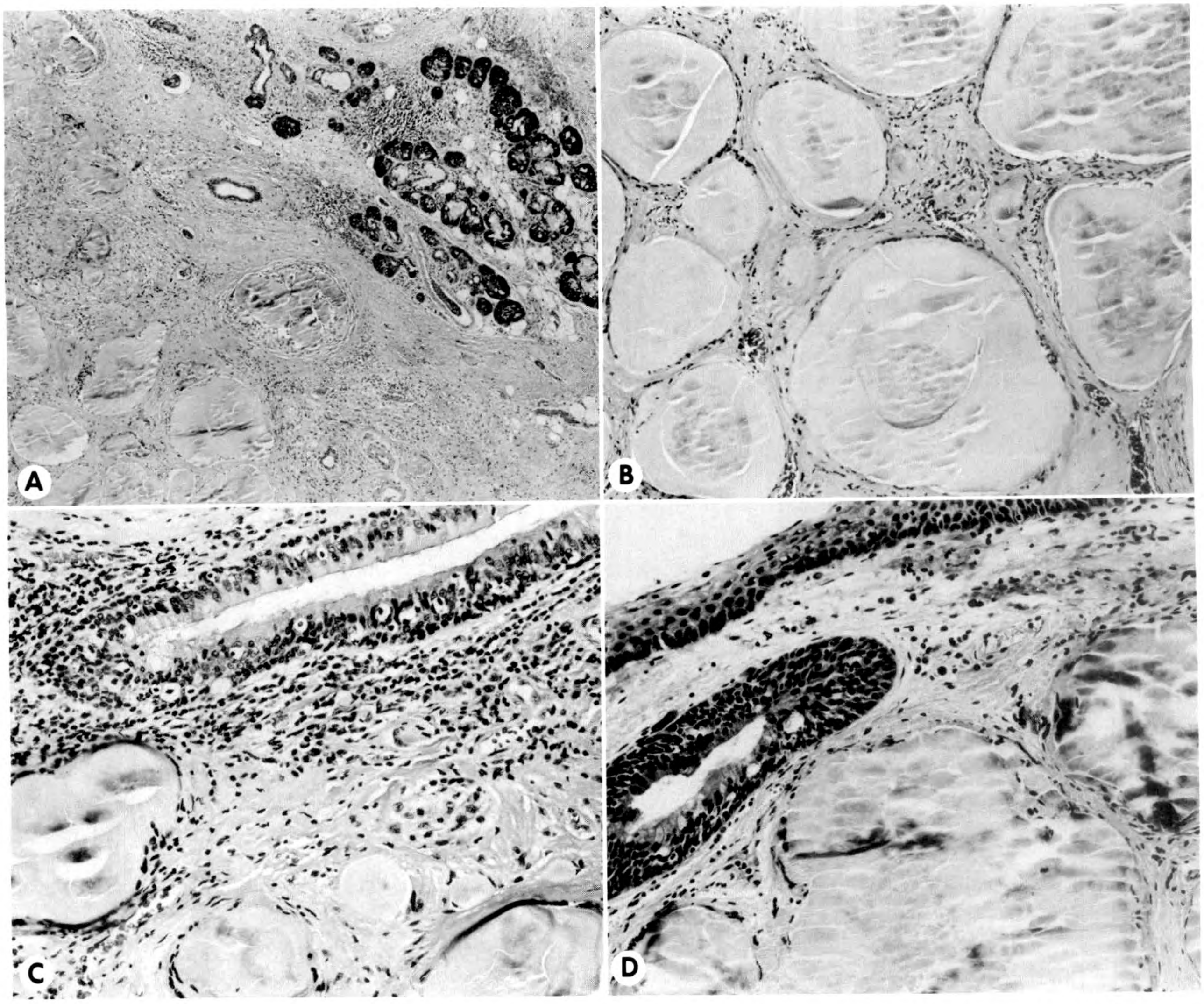
From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.



Amyloidosis of larynx. A) Localized (H & E, original x30). Amyloid lies in soft tissues about seromucous glands. B) Globular masses of amyloid in laryngeal lamina propria (H & E, original x140). C,D) Discrete amyloid masses in lamina propria (H & E, original x200). Amyloid may also provoke foreign body giant cell reaction (not shown).

and lymph nodes. When the localized amyloid protein has been defined, it has been the AL type.[1,8,9]

Oral Cavity. Symptoms and signs referable to amyloidosis in the oral cavity are rarely presenting features. The finding of a solitary intraoral amyloid deposit is rare.[9] The best-known oral finding is macroglossia, associated with primary systemic amyloidosis. When amyloid is present in the tongue, the patient is likely to also have amyloidosis with plasma cell dyscrasia.[9] The tongue is firm and indurated and may show a yellow nodularity along its lateral borders. The gingivae are usually diffusely involved, but can appear nearly normal on clinical examination. Elsewhere in the oral mucosa aphthous-type ulcers formed by rupture of hemorrhagic bullae, or macular or papular amyloid lesions may be found. Ten percent of patients with oral amyloidosis have an accompanying amyloidotic infiltration of their submandibular glands.

At considerable conflict are two reports of postmortem studies. Yamaguchi et al[9] claim an overall incidence of 36.4% of lingual amyloidosis in subjects older than 60 years. Van der Wal et al,[10] examining a similar number of tongues at necropsy, could not find a single case.

Sinonasal Cavities and Nasopharynx. Amyloidosis localized to these structures without an association with predisposing diseases is rare.[8] Presentation may be either diffuse or nodular, with the amyloid found around blood vessels, around salivary ducts, or as stromal masses. In nearly all instances there is an attendant diffuse chronic inflammatory reaction.

Larynx. The larynx is the most common site of involvement by amyloid in the head and neck, and localization in the larynx is twice as frequent as in any other part of the respiratory tract.[1,11,12] As in the nasopharynx and sinonasal tract, the subepithelial deposits are grossly diffuse or nodular. The supraglottic larynx, especially the false vocal cords, is the region most often involved, but the true vocal cords and subglottis are not spared. With respect to the true vocal cords, care must be taken to distinguish true amyloid from the pseudoamyloid so often found in vocal nodules. Pseudoamyloid has no fibrillary substance and is composed of an amorphous granular degeneration of ground substance with collagen fibers sparsely interspersed between fibroblasts.[12] Multifocality appears to be the norm in laryngeal amyloidosis. Seventeen of 22 Mayo Clinic patients had amyloid in multiple sites.[1] Extralaryngeal amyloid was found in 8 patients (trachea, nasopharynx, or nasal cavity). In the larynx, amyloid is most often in small ball-like masses or sheets, with or without vascular or minor salivary involvement (see Figure). The amyloid is AL (light chain, primarily of the λ type).[1]

A specific form of localized amyloidosis in the upper airway is that found in company with an extramedullary plasmacytoma — an association noted in some 20% of plasmacytomas.[12]

Lower Respiratory Tract. In this part of the airway, amyloidosis presents in three clinicopathologic forms: tracheobronchial, diffuse parenchymal, and nodular-parenchymal.[13] The lower trachea and bronchi are less involved than is the subglottic trachea.[11] Tracheobronchial involvement is more often diffuse rather than nodular and as a consequence has a poor prognosis.

CLINICAL IMPLICATIONS AND MANAGEMENT

Amyloidosis in any form is a slowly progressive lesion that does not respond to nonsurgical treatments. Abatement of the amyloid deposits may, however, follow control of the promoting and underlying disease.

As noted above, oral and sinonasal amyloidoses are usually but one manifestation of systemic diseases, pertinently plasma cell dyscrasias. On the other hand, laryngeal amyloidosis, as a presenting finding, is generally a localized process and is not associated with systemic diseases.[1] It is also noteworthy that systemic amyloidosis or a lymphoproliferative disorder did not subsequently develop in any of the 22 patients with amyloidosis of the larynx in the Mayo Clinic series.[1] Nonetheless, even when the amyloid is apparently restricted to the larynx, serum and urine electrophoresis and immunoelectrophoretic studies are recommended as parts of the clinical workup.[1]

"Localized" can be a deceptive adjective when applied to organ-related amyloidosis. This is particularly true when the amyloid is present as a diffuse infiltration of subepithelial tissues of the airway. Lewis et al[1] indicate endoscopic removal of the amyloid is adequate in most cases, and it can be repeated. Fourteen of their 22 (64%) patients had persistent or recurrent upper respiratory tract amyloidosis. Ten patients (45%) had multiple surgical procedures for local control. Only 1 of the patients died because of progressive (tracheobronchial) amyloidosis.

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OBITUARY

BRUCE PROCTOR, 1914-1992

Bruce Proctor, MD, died on May 22, 1992, of complications following a stroke. Born in Detroit, Michigan, on February 9, 1914, he spent most of his life in the area, attending the University of Detroit for 1 year and the University of Michigan for 2 years, then going to medical school at the latter institution, from which he received his medical degree in 1936. He completed his residency at the University of Chicago in 1941.

Bruce, as several physician friends have said, was truly "among the last of his kind." He bridged the gap between the preantibiotic and postantibiotic eras, between the all-sufficient physician of yesterday and the highly specialized one of today. In his earlier years, in private practice, he helped introduce laryngectomy to the Detroit area. Soon after World War II ended, he traveled with Dr Harold Schuknecht to Europe, spending several weeks with Drs Wullstein and Zollner, for the purpose of introducing tympanoplasty concepts in the United States.

One of the few multitalented surgeons, he was equally adept at radical neck and acoustic neuroma surgery and hypophysectomy. He loved to explore foreign literature and wrote tympanoplasty reviews for many years. Although he enjoyed horticulture, farming, fishing, and hunting, his favorite hobby was anatomy. He wrote one of the first surgical anatomy books on otology for our specialty.

Bruce could treat every conceivable otolaryngologic disorder by himself, aided by his unsurpassed knowledge of anatomy, often performing over 20 surgical procedures in a single day. His familiarity with the world literature was also spectacular, and he could speak for hours on any medical subject. He was fascinated with world history and often amazed ministers, rabbis, and priests with his vast knowledge of historical Christianity and Judaism.

He especially enjoyed teaching and encouraging residents, spending many hours with them in the operating room and anatomy laboratory. He enjoyed traveling around the world, giving talks and presenting courses in anatomy.

Many of the great industrialists of the Midwest were his friends. Among these was Stanley Kresge, then president of the Kresge Foundation, started by his father, Sebastian Kresge. Between Bruce and Mr Kresge, the idea of a Hearing Institute was raised. Because there was already established an Eye Institute in Detroit, Bruce approached Dr A. C. Furstenberg, then Dean of the University of Michigan Medical School and Chairman of the Department of Otolaryngology, about establishing an institute for hearing research at the University of Michigan with money from the Kresge Foundation. This was established in short order, so Bruce presented his ideas to Merle Lawrence, chairman of the building committee and subsequently Director of the Kresge Hearing Research Institute. Bruce continued his interest in the Institute's programs and gave its activities his full support. Until his death Bruce was working on discriminating more details of the infratemporal fossa and round window niche.

Like the old-fashioned country doctor, Bruce was not only an extremely well-rounded and dexterous physician, but a very loving and caring one. He is survived by his wife, two children, eight grandchildren, and 10 great-grandchildren. Two of them have followed in his footsteps: his son, Conrad A. Proctor, MD, and a grandson, Todd Proctor, MD, now a resident, both in otolaryngology.

Bruce Proctor lived an exemplary Christian life and will be missed by his family, patients, friends, and colleagues.

Conrad A. Proctor, MD
Merle Lawrence, PhD

LETTERS TO THE EDITOR

To the Editor:

Drs Brownlee and Shockley present an interesting paraganglioma occurring "off the beaten track" (Thyroid Paraganglioma, *Ann Otol Rhinol Laryngol* 1992;101:293-9). This case was originally diagnosed as a thyroid medullary carcinoma. They correctly note that Lawson and Zak's[1] autopsy study reveals the inferior laryngeal paraganglia to be situated 1) on the inner surface of the cricoid, 2) on the outer cricoid surface, 3) embedded in the cricothyroid ligament, or 4) within the thyroid capsule.[2] The variable position of the inferior laryngeal paraganglia accounts for the variable presentation of the rare tumors that arise from them: 1) as purely subglottic tumors, 2) as dumbbell-shaped tumors with an intraluminal and a subthyroidal component,[3] or 3) as entirely subthyroid tumors situated beneath the thyroid capsule.

The authors, too, point out (in the third from last paragraph) that all of these tumors should be called "inferior laryngeal paragangliomas," which is a more accurate reflection of their origin. Therefore, entitling this article "Thyroid Paraganglioma" is misleading. The thyroid parenchyma has not been shown to have paraganglionic tissue.

One further point: critical review of the alleged "25% malignancy rate" in laryngeal paragangliomas[4] reveals many of these cases to actually be *neuroendocrine* carcinoma.[5] Therefore no comparison can be made between the "malignant potential" of superior versus inferior laryngeal paragangliomas.

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Margie Brandwein, MD
Departments of Pathology and
Otolaryngology
Mount Sinai School of Medicine
One Gustave L. Levy Pl
New York, NY 10029-6574

To the Editor:

Thank you for the opportunity to respond to Dr Brandwein's observations and comments. As stated in our paper (*Ann Otol Rhinol Laryngol* 1992;101:293-9), we believe that the presentation of a paraganglioma is determined more by the anatomic location of the paraganglia from which it arises than by its "biologic behavior."[1]

In reference to our title, "Thyroid Paraganglioma," as misleading, we discussed changing the title prior to submitting the manuscript for publication, but decided to leave it as it was. We agree that it might cause some confusion, but our hope was that others searching for reports of what they consider to be thyroid paraganglioma would easily reference our article and its conclusions (ie, that these are actually inferior laryngeal paragangliomas).

As to Dr Brandwein's last point, concerning superior and inferior laryngeal paraganglioma, her concerns are certainly valid. In our discussion, we were suggesting possible differences that need to be examined as the number of reported cases of both increase. Although we reported that the incidence of malignancy in laryngeal paraganglioma "is as high as 25%,"[2] we also pointed out that other authors "believe the incidence to be overestimated."[3,4] Dr Barnes's study[5] was not available to us at the time this paper was written.

We agree that this is often a difficult diagnosis to make and that many reported malignant paragangliomas are misdiagnosed carcinomas, as mentioned in our review and elsewhere.[3,4] In general, laryngeal paragangliomas behave in a benign fashion, with little tendency to invade or metastasize.

We thank Dr Brandwein for her interest and comments and look forward to reading her upcoming article.

Richard E. Brownlee, MD
Department of Otolaryngology–
Head and Neck Surgery
University of Florida
Gainesville, FL 32608

William W. Shockley, MD
Department of Otolaryngology–
Head and Neck Surgery
University of North Carolina
Chapel Hill, NC 27599-7070

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To the Editor:

Regarding the paper "Rosai-Dorfman Disease Involving the Premaxilla" by Shemen et al (*Ann Otol Rhinol Laryngol* 1991;100:845-51), please be advised that I have recently been informed by Dr Bruce Wenig of the Armed Forces Institute of Pathology that our pathologist, Dr Toth, originally submitted the case to the AFIP prior to Dr Rosai and that Dr Wenig, in fact, first ascertained the correct diagnosis. His invaluable contribution should therefore be noted.

Larry Shemen, MD
233 E 69th St, Suite 1D
New York, NY 10021

INSTRUCTIONS TO AUTHORS

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Send manuscripts to Editor Brian F. McCabe, MD, Department of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242. Original manuscripts dealing with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck medicine and surgery, maxillofacial and plastic surgery, audiology, speech pathology, and related specialties are considered for publication. All materials submitted for publication undergo peer review.

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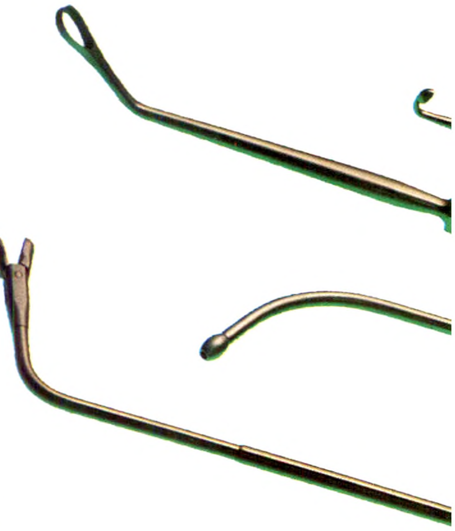

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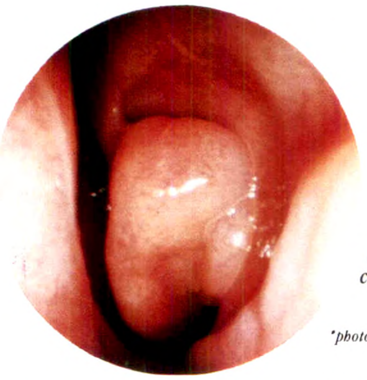
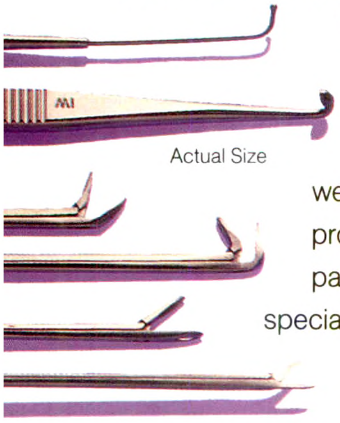


*Concha bullosa on left side bulging into lateral nasal wall. Entrance to middle meatus blocked and a polyp is arising from the contact area.**

**photo by Professor H. Stammberger*



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VOLUME 101 NOVEMBER 1992 NUMBER 11

CONTENTS

FROM THE AMERICAN LARYNGOLOGICAL ASSOCIATION

Point-Touch Technique of Botulinum Toxin Injection for the Treatment of Spasmodic Dysphonia
David C. Green, MD; Gerald S. Berke, MD; Paul H. Ward, MD; Bruce R. Gerratt, PhD 883

FROM THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

Quantitative Mapping of the Effect of Botulinum Toxin Injections in the Thyroarytenoid Muscle
Elaina F. George, MD; Marc Zimbler; Bei-Lian Wu, MD; Hugh F. Biller, MD; Ira Sanders, MD 888

Continuous Positive Airway Pressure as a Promoter of Laryngospasm During Halothane Anesthesia
David A. Silva, MD; Ira Sanders, MD 893

Laryngotracheal Reconstruction in Adults With the Sternocleidomastoid Myoperiosteal Flap
Michael Friedman, MD; Amy D. Mayer, MD 897

INDEPENDENT CONTRIBUTIONS

Detection of Regulatory Factors of Lymphokine-Activated Killer Cell Activity in Head and Neck Cancer Patients Treated With Interleukin-2 and Interferon Alpha
Gary L. Clayman, DDS, MD; Gregory Young, MD; Dorothy L. Taylor, MS; Howard E. Savage, PhD; Pierre Lavedan, MD; Stimson P. Schantz, MD 909

Bilateral Choanal Atresia Associated With Malformation of the Anterior Skull Base: Embryogenesis and Clinical Implications
Michael E. Dunham, MD; Robert P. Miller, MD 916

Laryngeal Adenocarcinoma, Not Otherwise Specified, Treated With Carbon Dioxide Laser Excision and Postoperative Radiotherapy
Phillip J. Haberman, MD; Rex S. Haberman II, MD 920

Facial Canal Dehiscence: Histologic Study and Computer Reconstruction
Haruo Takahashi, MD; Isamu Sando, MD, DMSc 925

Immunohistochemical Analysis of the Cytokeratin Expression in Middle Ear Cholesteatoma and Related Epithelial Tissues
Daniël Broekaert, PhD; Paul Coucke, PhD; Sabine Leperque, MD; Frans Ramaekers, PhD; Goos Van Muijen, PhD; Dirk Boedts, MD; Irene Leigh, MD; Birgitte Lane, PhD 931

Skull Base Dumbbell Tumor: Surgical Experience With Two Adolescents
Roland D. Eavey, MD; Parviz Janfaza, MD; Paul H. Chapman, MD; Brooke Swearingen, MD; Norbert Liebsch, MD; Alfred Weber, MD; Kenneth R. Davis, MD; William S. Ferguson, MD 939

Syndrome of Inappropriate Secretion of Arginine Vasopressin in Patients With Cancer of the Head and Neck
Yoav P. Talmi, MD; Henry T. Hoffman, MD; Brian F. McCabe, MD 946

Rat Model for a Vascularized Laryngeal Allograft
Scott Strome, MD; Erik Sloman-Moll, MD; Bernadette R. Samonte; Justin Wu; Marshall Strome, MD 950

SOFTWARE REVIEW

The TMJ Scale: Including a Computer Program Disk and 74-Page Illustrated Manual
Carl M. Nechtman, MD 954

IMAGING CASE STUDY OF THE MONTH

Magnetic Resonance Angiography of Synchronous Bilateral Carotid Body Paragangliomas and Bilateral Vagal Paragangliomas
MAJ Moises A. Arriaga, MC, USAF; William W. M. Lo, MD; Derald E. Brackmann, MD 955

PATHOLOGY CONSULTATION

Embryoma (Sialoblastoma) of Salivary Glands
John G. Batsakis, MD; Robert Frankenthaler, MD 958

MISCELLANEOUS

Instructions to Authors 11a

Information for Subscribers 16a

Statement of Ownership 17a

Index to Advertisers 18a

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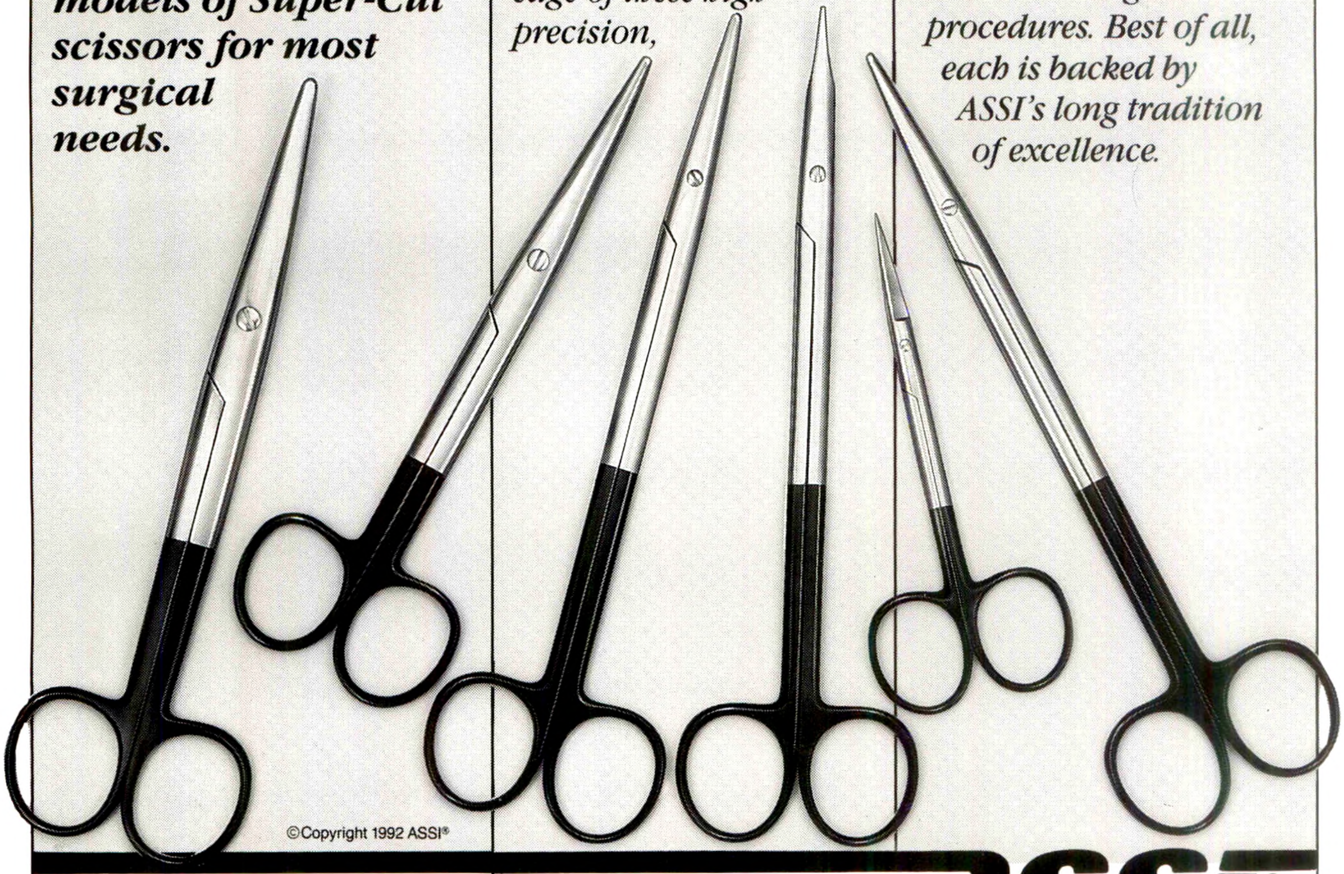

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Brian F. McCabe, MD
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POINT-TOUCH TECHNIQUE OF BOTULINUM TOXIN INJECTION FOR THE TREATMENT OF SPASMODIC DYSPHONIA

DAVID C. GREEN, MD
SEATTLE, WASHINGTON
PAUL H. WARD, MD
LOS ANGELES, CALIFORNIA
GERALD S. BERKE, MD
LOS ANGELES, CALIFORNIA
BRUCE R. GERRATT, PHD
LOS ANGELES, CALIFORNIA

Intralaryngeal injections of botulinum toxin (Botox), under electromyographic guidance, have emerged as an effective treatment for adductor spasmodic dysphonia. To remain effective, these injections must be repeated every 3 to 9 months as the symptoms recur. One drawback to the current method is the need for electromyographic confirmation of needle placement into the thyroarytenoid muscle. This report describes an anatomic approach to Botox injection that requires only flexible nasopharyngeal endoscopy and careful evaluation of the anatomic landmarks. This technique has been used successfully on 13 patients, and objective pretreatment and posttreatment measures are reported.

KEY WORDS — botulinum injection, laryngeal dystonia, spastic dysphonia.

INTRODUCTION

Spasmodic dysphonia is a serious voice disorder characterized by a strained or strangled voice, and it often interrupts the fluency of continuous speech. Since the first description of the disorder by Traube[1] in 1871, its exact cause and treatment have been the subject of controversy.

In the past, this disorder was thought to reflect psychiatric problems. More recently, Blitzer et al[2] found through clinical and electromyography (EMG) evaluation that many patients with "spastic dysphonia" actually have a dystonia. Dystonia is a neurologic disorder of motor control processing characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms. The cause is usually idiopathic. The dystonia may be restricted to the larynx or present in other areas of the body as well, such as blepharospasm.[2]

There are a variety of treatments for adductor spastic dysphonia, which include speech therapy, psychotherapy, biofeedback, systemic medicine, nerve section, botulinum toxin (Botox) injection, and thyroplasty. Dedo[3] was the first to describe recurrent laryngeal nerve section as a treatment for spastic dysphonia. The aim was to achieve a voice that was slightly breathy but easier to produce. After a 3-year follow-up, his group[4] reported a 10% to 15% recurrence rate according to patient self-evaluations. Aronson and DeSanto[5] reported an initial success rate of 97% at 6 months for recurrent laryngeal nerve section. This success rate fell to 36% at 3 years' follow-up. The failures showed gradual hyperadduction of the intact vocal fold against the paralyzed fold. This was thought to be due to a worsening of the patient's underlying neurologic condition.

Biller et al[6] reported, in 1979, crushing the recurrent laryngeal nerve as a treatment for spastic dysphonia. Although all patients had initial improvement, only 13% were improved at 3 years' follow-up.[7]

Blitzer et al[8,9] reported the first series of patients with focal laryngeal dystonia to be treated with local vocal fold injection of Botox. This toxin acts presynaptically at nerve terminals to prevent calcium-dependent release of acetylcholine, which results in muscle paralysis. There were five patients in their series, and all, within 2 to 3 days, experienced benefit that lasted 3 to 6 months. Although the authors initially injected only one vocal fold, they now perform bilateral injections. There were no systemic side effects from the injections, but they state that the long-term systemic or local laryngeal effects are unknown.

Using EMG, Ludlow et al[10] studied patients with adductor spastic dysphonia who failed unilateral recurrent laryngeal nerve section. They found that some of the failures were due, at least in part, to reinnervation of the thyroarytenoid muscle by the previously sectioned recurrent laryngeal nerve, and that compensation by the nonoperated side may have

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From the Division of Head and Neck Surgery, University of California at Los Angeles, and the West Los Angeles Veterans Administration Medical Center, Los Angeles, California.

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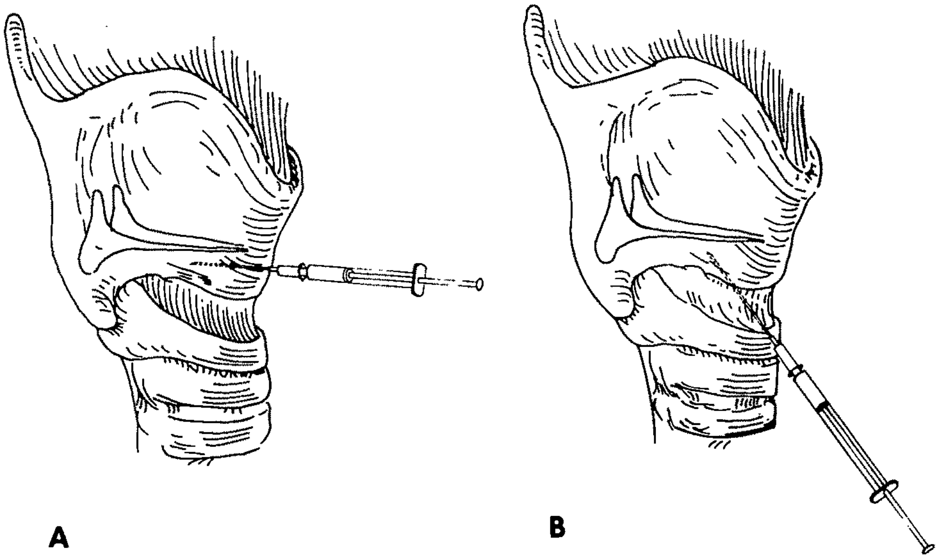

Location and direction of needle placement for transcutaneous injection of botulinum toxin into ipsilateral thyroarytenoid muscle. A) Through thyroid cartilage. B) Through cricothyroid membrane.

played a role in others.[10] They treated these patients successfully with Botox injections.

Initial reports of Botox injections of the true vocal fold have relied on EMG localization of the thyroarytenoid muscle for injection. Recently, Ford et al[11] described an indirect laryngoscopic approach to Botox injection in which all patients studied demonstrated objective improvement after injection.

The technique for transcutaneous injection of the vocal fold was first described in connection with Teflon injections as a treatment for unilateral vocal fold paralysis.[12] Ward et al[13] described insertion of a needle through the cricothyroid membrane into the subglottic space with monitoring of the actual fold injection through a fiberoptic nasopharyngoscope or a Hopkins rod laryngoscope. Hirano et al[14] described a transcutaneous vocal fold injection technique in which the needle is inserted through the cricothyroid membrane directly into the edge of the vocal fold.

This report describes a relatively safe and accurate transcutaneous method of Botox injection that requires only flexible nasopharyngeal endoscopy.

METHODS AND SUBJECTS

Injection Technique. The patient was seated in an examination chair. Palpation of the neck was used to mark the outline of the thyroid and cricoid cartilage on the anterior neck skin with a surgical marking pen.

The nose and pharynx were topically anesthetized with lidocaine 2% spray. A flexible nasopharyngoscope (Olympus, Los Angeles, Calif) was passed through the nose into the hypopharynx to visualize the true vocal folds. The fiberscopic laryngeal image was viewed on a television screen and recorded on videotape.

The cutaneous needle injection site was prepared with alcohol. The injection was given with a 2-mL syringe and a 1.5-in 27-gauge needle. The injected material was botulinum A toxin (Oculinum Inc, Berkeley, Calif) that was supplied as a freeze-dried residue of the toxin at a concentration of 50 ng per vial (140 U). The freeze-dried toxin was stored at –20°C and reconstituted with 0.9% saline at a concentration of 25 U/mL and used immediately.

The injection was given through the thyroid cartilage into the ipsilateral thyroarytenoid muscle unless the cartilage was ossified (see Figure, A). The needle was oriented at 90° to the skin of the neck and directed posteriorly in the sagittal plane. From the previously marked outline of the thyroid cartilage the approximate location of the anterior commissure of the vocal folds was estimated as midway between the thyroid notch and the bottom edge of the thyroid cartilage, in the midline.[15] The needle was placed 5 mm lateral and 5 mm inferior to this point. No previous or concurrent injections of local anesthetic were required. The accuracy of needle placement is assured by pointing the needle, on the basis of anatomic landmarks, into the ipsilateral thyroarytenoid muscle. The correct depth of needle penetration is judged by sensing the depth at which the needle passes through the thyroid cartilage to permit easy injection of toxin. While the needle is within the cartilage, injection pressures are high because of the density of the cartilage matrix. With further penetration, the injection pressure becomes low as the needle enters the thyroarytenoid muscle. We have termed this method the point-touch technique. Adequate needle positioning is confirmed through the flexible nasopharyngoscope before injection. Initially, 5 U of toxin was injected bilaterally by the point-touch technique. However, 2 U is routinely given now in order to

INITIAL 13 PATIENTS TREATED BY PERCUTANEOUS BOTOX INJECTION USING POINT-TOUCH OR CRICOTHYROID TECHNIQUE

Patient No.	*Length of Symptoms (y)*	*Previous Injection or Surgery*	*Dose and Technique*	*Vocal Fold Motion*	*Response Time (mo)*	*Pre/Post Glottic Resistance (cm H_2O per liter per second)*	*Pre/Post Jitter (%)*	*Adverse Reactions*
1	2		5 U bilat PT	Normal	3	60/43		
2	7		5 U bilat PT	Bowing	5	69/32	3	Breathy for 2 wk
3	7		4 U bilat PT	Normal	3	80/42	2	
4	6	Botox	2 U bilat PT	Bowing	4	63/28		Breathy for 4 wk
5	7		15 U CT	L fold paresis	5	76/42	1	Breathy for 4 wk
6	10	R RLN section	4 U R fold, no response; 2 U L fold, PT 1 wk later	L fold normal	6	75/37		
7	5		2 U bilat PT	Normal	5	83/42		Breathy for 2 wk
8	6		2 U bilat PT	Normal	6	90/50		2 wk before improvement
9	5	Botox	2 U bilat PT	Normal	5			
10	6	Botox	1 U bilat PT	Normal	2			
11	5		2 U bilat PT	Normal	5	72/40	4	
12	10		15 U L fold CT	L fold paralysis	4	70/—		
13	10		2 U bilat PT	Bowing	4	84/40		Breathy for 3 wk

RLN — recurrent laryngeal nerve, PT — point-touch trans–thyroid cartilage technique, CT — cricothyroid membrane technique.

reduce the incidence of vocal fold bowing and breathiness.

If the thyroid cartilage could not be penetrated with the needle because of ossification, the injection was performed through the cricothyroid membrane (see Figure, B). In this case, the needle was placed just under the edge of the thyroid cartilage, approximately 1.5 cm from the midline, and directed superiorly, medially, and posteriorly. The proper depth of penetration and accuracy of needle placement into the ipsilateral thyroarytenoid muscle were monitored through the flexible nasopharyngoscope. Patients undergoing transcutaneous cricothyroid injection routinely receive 15 U into one vocal fold.

Subjects and Evaluation of Vocal Function. During the period April 1990 to October 1991, a total of 13 patients (5 men and 8 women) with a diagnosis of adductor spasmodic dysphonia underwent transcutaneous intrafold injection. The Table describes these 13 patients. The length of symptoms varied from 2 years to 10 years. Three of the 13 patients had undergone previous Botox injection with EMG control. One patient had previously undergone a right recurrent laryngeal nerve section. The usual dose for most patients was 2 U. Three patients developed vocal fold bowing after injection, and 2 patients after cricothyroid injection developed a fold paresis or paralysis.

Each patient was evaluated by an otolaryngologist and a speech pathologist. Ten of the 13 patients had previously seen a neurologist. Their ages ranged from 32 to 74 years with a mean of 50 years. Eleven of 13 patients underwent preinjection vocal function evaluation consisting of laryngostroboscopy, acoustic analysis of sustained phonation, and laryngeal resistance estimation. In addition, a 1-minute speech monologue was recorded. Of these 13 patients, 4 had acoustic measurements both before and after Botox injection, consisting of jitter of the vowel /a/. Ten of the 13 patients underwent both preinjection and postinjection evaluation of laryngeal resistance by the technique described by Smitheran and Hixon[16] with a modification: to reduce the chance that quick fluctuations in phonation influenced the results, we averaged the amplitude of the airflow signal over the steady-state, vocalic portion of the syllables, rather than measuring the amplitude of one point in the middle of the syllable.

For stroboscopic imaging of the larynx, a Bruel & Kjaer laryngostrobe unit (model 4914, Orange, Calif) was used. The stroboscope was connected to a Wolf 90° telescope via a fluid-filled light cable. The image was detected by a Toshiba CCD (charge-coupled device) video camera (Toshiba IK-C30A, Buffalo Grove, Ill) and a Sony U-matic videocassette recorder (Sony, VO-9850, Teaneck, NJ).

RESULTS

Videostroboscopy and Jitter. The preinjection analysis of all 13 patients with adductor spasmodic dysphonia demonstrated complete glottic closure with episodes of glottic spasm and supraglottic overclosure during phonation. The true vocal folds had full symmetric abduction and adduction. All patients demonstrated frequent, intermittent periods of strained vocal quality with occasional episodes of aphonia interrupting speech fluency.

Response to the injection lasted from 2 months to 6 months. Perceptually, all 13 patients had an increase in speech fluency and were pleased with the result. Moreover, they have all returned for subsequent injections. The Table presents subject information and results after injection. Our findings indicate the 95% confidence interval of vocal tract resistance is 37 to 51 cm H2O per liter per second for normally speaking men and 41 to 57 cm H2O per liter per second for normally speaking women. (See similar normative results reported by Netsell et al.[17]) Although normative values for laryngeal resistance varied with sex and age, 10 of the 11 patients evaluated for laryngeal resistance demonstrated elevated laryngeal resistance before injection. Nine of these 10 subjects returned to the normal range 4 weeks after injection. The Table also compares the preinjection and postinjection percent jitter for 4 of the 13 injected patients. Three of the 4 patients had a decrease in jitter after injection. The one patient with an increase in jitter qualitatively demonstrated a breathy voice, although with increased fluency in continuous speech. The mean preinjection jitter for these 4 patients was 2.08%, compared to the postinjection value of 0.682%. There were no patients in this group with a posterior glottic chink leak during phonation after injection.

Complications. There were no airway complications or infectious complications from this method. All patients, immediately after injection, had a mild degree of true vocal fold edema that resolved. There were no cases of postinjection aspiration. The major adverse reaction included breathiness, lasting a maximum of 4 weeks in 5 of the 13 patients. One patient noted improvement 2 weeks after the injection, rather than the typical 36 hours.

DISCUSSION

The Botox injections paralyze the thyroarytenoid muscle by blocking the release of acetylcholine from the presynaptic nerve terminals of the recurrent laryngeal nerve. Using a canine model of laryngeal hyperadduction, Green and Berke[18] have shown that hyperadduction can be reduced through selective thyroarytenoid muscle paralysis alone. The unilateral absence of thyroarytenoid contraction (despite a vocal fold in the adducted position) allowed the intraglottic and subglottic pressures to fall during phonation.

During their initial experience, Miller et al[19] described two patients with unilateral vocal fold adductor paralysis after Botox injection of 20 and 30 U. This was thought to be due to migration of the toxin to the lateral cricoarytenoid muscle. The posterior cricoarytenoid muscle was not affected. Brin et al[20] noticed sluggish vocal fold motion with injection doses of 7.5 U. They were able to achieve selective thyroarytenoid muscle paralysis and reduce the degree of overall fold paralysis by injecting both folds with a reduced dose of 3.75 U. The point-touch technique presented in this report was also able to achieve selective thyroarytenoid muscle paralysis bilaterally with preservation of vocal fold adduction and abduction. It should be noticed that the three patients who had previously undergone Botox injection using EMG-guided injection underwent injection of the same number of units using the point-touch technique with the same effective response.

This study found subjective perceptual improvements in speech fluency in all patients after injection. Also, all patients evaluated before and after injection in this study showed improvement in laryngeal resistance with this technique. In one patient, the improvement in fluency was not accompanied by a decrease in jitter because of an increase in the breathiness of the patient's phonation after injection. This patient was pleased with the result despite the increase in jitter. This problem emphasizes the need to examine a wide variety of speech variables, including measures of continuous speech and pitch breaks, to more fully document patients' speech.

The optimal treatment for spasmodic dysphonia, like its fundamental cause, has yet to be found. Until more is known about the disorder, treatments will continue to be directed at the laryngeal symptoms it produces. Although Botox injections do improve the patient's ability to phonate, the improvement is not permanent. Reinjection is required every 3 to 6 months.

The advantages of the transcutaneous injection of Botox are as follows.

1. No EMG equipment or EMG technician is required.
2. The working distance is shorter than the transoral route.

3. Patients with a sensitive gag reflex or difficulty with full mouth opening can be injected.

The disadvantages are as follows:

1. The procedure requires a flexible nasopharyngoscope.
2. A second person is required to hold the nasopharyngoscope during injection.
3. In obese patients the external laryngeal landmarks may be difficult to locate.
4. Successful placement of the needle requires a working knowledge of the intralaryngeal position of the thyroarytenoid muscle as discerned from external laryngeal landmarks.

Efforts have been made to obtain permanent selective bilateral paralysis of the thyroarytenoid muscle surgically. Carpenter et al[21] divided the adductor branch of the recurrent laryngeal nerve in dogs and humans. This procedure was able to preserve the abductor movement of the vocal fold, but eliminated the adductor movement, as well as thyroarytenoid muscle contraction. This operation holds out the promise of a permanent selective denervation of the thyroarytenoid muscle. In the interim, the point-touch technique of Botox injection will allow patients with spasmodic dysphonia to be effectively treated by otolaryngologists within their own communities.

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QUANTITATIVE MAPPING OF THE EFFECT OF BOTULINUM TOXIN INJECTIONS IN THE THYROARYTENOID MUSCLE

ELAINA F. GEORGE, MD
MARC ZIMBLER
BEI- LIAN WU, MD
HUGH F. BILLER, MD
IRA SANDERS, MD
NEW YORK, NEW YORK

Spasmodic dysphonia has been successfully treated by thyroarytenoid muscle injections of botulinum toxin (Botox) with dosages ranging from 0.625 to 25 U. In some patients, excessive paralysis with resulting breathiness and aspiration have been noted. In order to maximize the efficiency of Botox injections, the histologic effects of various Botox dosages were examined in the dog. Nine canine thyroarytenoid muscles were injected with 0.5 to 12.5 U of Botox. After 24 hours, the recurrent laryngeal nerve to the injected muscle was electrically stimulated in order to deplete the glycogen within the muscle fibers. Frozen sections of this muscle were then stained for glycogen. Those fibers that retained their glycogen were presumed paralyzed by the Botox injection. The extent of paralysis was found to be dose-related from 1.0 to 7.5 U. At 10 U and above the muscle was completely paralyzed. Spread of the toxin to the lateral cricoarytenoid muscle was seen at doses as low as 1.0 U. Clearly, doses less than 10 U appear sufficient for clinical paralysis.

KEY WORDS — botulinum toxin, injection, mapping.

INTRODUCTION

Spasmodic dysphonia has been characterized as a disorder of central motor processing. Two main types have been described: the adductor type, characterized by involuntary paroxysmal spasms of the vocal cords leading to strained-strangled phonation, and the abductor type, characterized by intermittent hyperabduction of the vocal cords leading to a whispered voice.[1] Therapies such as systemic pharmacologic agents, hypnosis, and speech therapy have all proven ineffective in the treatment of spasmodic dysphonia. However, one innovative treatment of the adductor type was initially adopted. It involved unilateral sectioning of the recurrent laryngeal nerve in an attempt to relieve the spasms and facilitate speech.[2] This method has fallen into disfavor, however, because in many cases symptoms returned. In fact, some patients had more severe symptoms, presumably due to hyperfunction of the nonparalyzed vocal cord.[3,4]

Recently, botulinum toxin (Botox) has emerged as the most effective method of treatment for spasmodic dysphonia. Since Scott[5] introduced Botox for the treatment of strabismus in 1981, chemical denervation with Botox has been applied to treat a wide range of dystonias, including torticollis,[6,7] blepharospasm,[8] hemifacial spasm,[9,10] detrusor-sphincter dyssynergia,[11] hand dystonia,[12] oromandibular and lingual dystonia,[13] sixth nerve palsy,[14] anismus,[15] and, more recently, cerebral palsy[16] and stuttering.[17]

Botox binds to receptors on the presynaptic terminal. Once there, it inhibits the release of acetylcholine, thereby functionally denervating the muscle. In fact, the chemical denervation caused by Botox mimics the physiologic events that take place following axotomy, including atrophy, the appearance of extrajunctional acetylcholine receptors, and the maintenance of end plate potentials.[18]

Currently, most clinical therapy involves placing a hollow bore electromyography needle through the cricothyroid membrane into the thyroarytenoid (TA) muscle. Either low doses (0.625 to 2.5 U) of the toxin are injected into both vocal cords[17] or higher doses (15 to 25 U) are injected into a single vocal cord.[13] With percutaneous injections, placement of the injection is determined by electromyographic guidance. The site for injection is chosen by the presence of potentials evoked when the patient phonates or performs the Valsalva maneuver.[19] Although this ensures that the needle is somewhere in the TA muscle, there is no way of knowing where the needle is along the length of the muscle. Recently some investigators have used a peroral injection technique that allows visualization of the needle by indirect laryngoscopy.[20,21] Theoretically, this technique allows more accurate placement of the Botox. Both the

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REPRINTS — Ira Sanders, MD, Dept of Otolaryngology, Box 1189, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

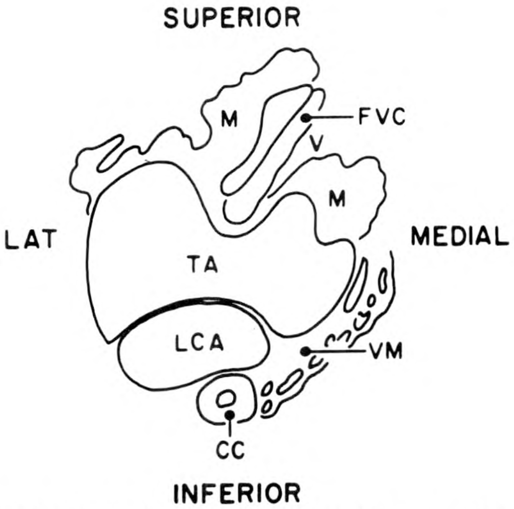

Fig 1. Schematic of orientation and components of thyroarytenoid muscle (TA) sections. M — mucosa, V — ventricle, FVC — false vocal cord, VM — vocal cord mucosa, LCA — lateral cricoarytenoid muscle, CC — cricoid cartilage.

percutaneous and peroral techniques can result in excessive weakness of the adductor muscles. This is manifested by breathiness and aspiration.[18] In addition, antibody formation has been reported at high doses of Botox.[22]

Many clinical trials have made qualitative determinations of the toxin's efficacy, but there has been little work done on the quantitative effect of the toxin. Clinicians have essentially taken a trial and error approach, and have been titrating the toxin to achieve the desired effects. Hence, the length of the toxin's effect and the reproducibility of the results vary. The purpose of this experiment was to apply a new technique that quantitates the effect of Botox.

Prolonged electrical stimulation of a nerve to a muscle simulates mechanical exercise, and results in glycogen depletion of that muscle's individual fibers. Glycogen depletion thus provides a marker of muscle fatigue. Our preliminary studies on the rat tibialis anterior muscle[23] demonstrated this phenomenon. We injected the toxin into the tibialis anterior and stimulated the common peroneal nerve. The muscle was then stained for glycogen by using periodic acid–Schiff reagent (PAS). As expected, the glycogen of muscle fibers not exposed to Botox was depleted by stimulation, and therefore did not stain with PAS. Conversely, those fibers with end plates chemically denervated by Botox were heavily stained by PAS. Because the area of paralysis was equivalent to the spread of the toxin, it was possible to quantitate the effects of Botox by measuring the area of glycogen retention with a computerized digitized tablet. The tibialis muscle was chosen because of its easy surgical accessibility and the predominance of type 2 (fast twitch) fibers, which are also found in the TA muscle of the human vocal cord. In short, by measuring the area of glycogen retained after exposure to the toxin, we were able to map the area of effective toxin action, and with microscopic study had a simple yet precise way to quantitate the pharmacologic action of the toxin.

We chose to apply our technique to the dog TA muscle because it more closely parallels the clinical application for the treatment of spasmodic dysphonia. Our technique only provides a two-dimensional representation of the toxin's kinetics. It is also possible that artifact was introduced by histologic preparation somehow, leading to an underestimation of the paralysis that would be seen in the human TA muscle at comparable doses. By using the dog TA muscle as a model, we hoped to provide information that will enable Botox to be used more efficiently at lower doses and with fewer complications, and perhaps

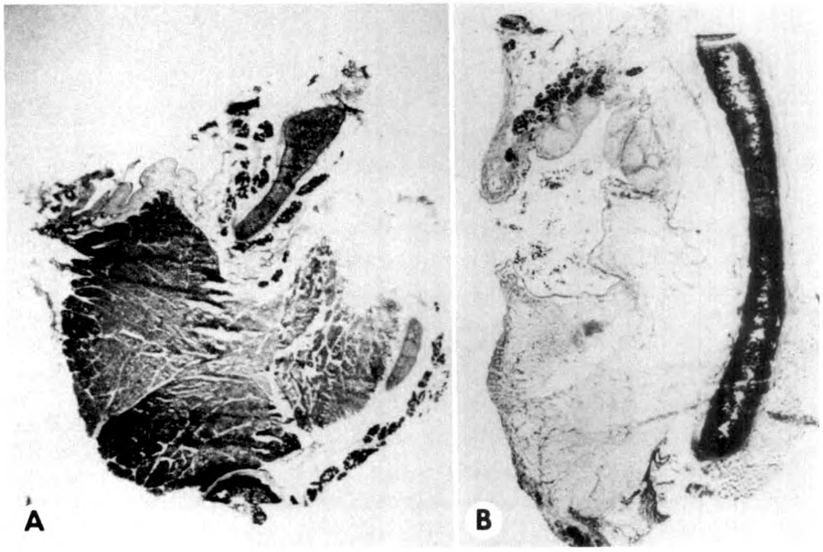

Fig 2. Controls. A) This section has been stained for glycogen without having been subjected to electrical stimulation or botulinum injection. Note homogeneous dark staining of thyroarytenoid muscle and lateral cricoarytenoid muscle. B) This specimen has been electrically stimulated prior to undergoing staining for glycogen. Note that all muscle fibers are homogeneously pale.

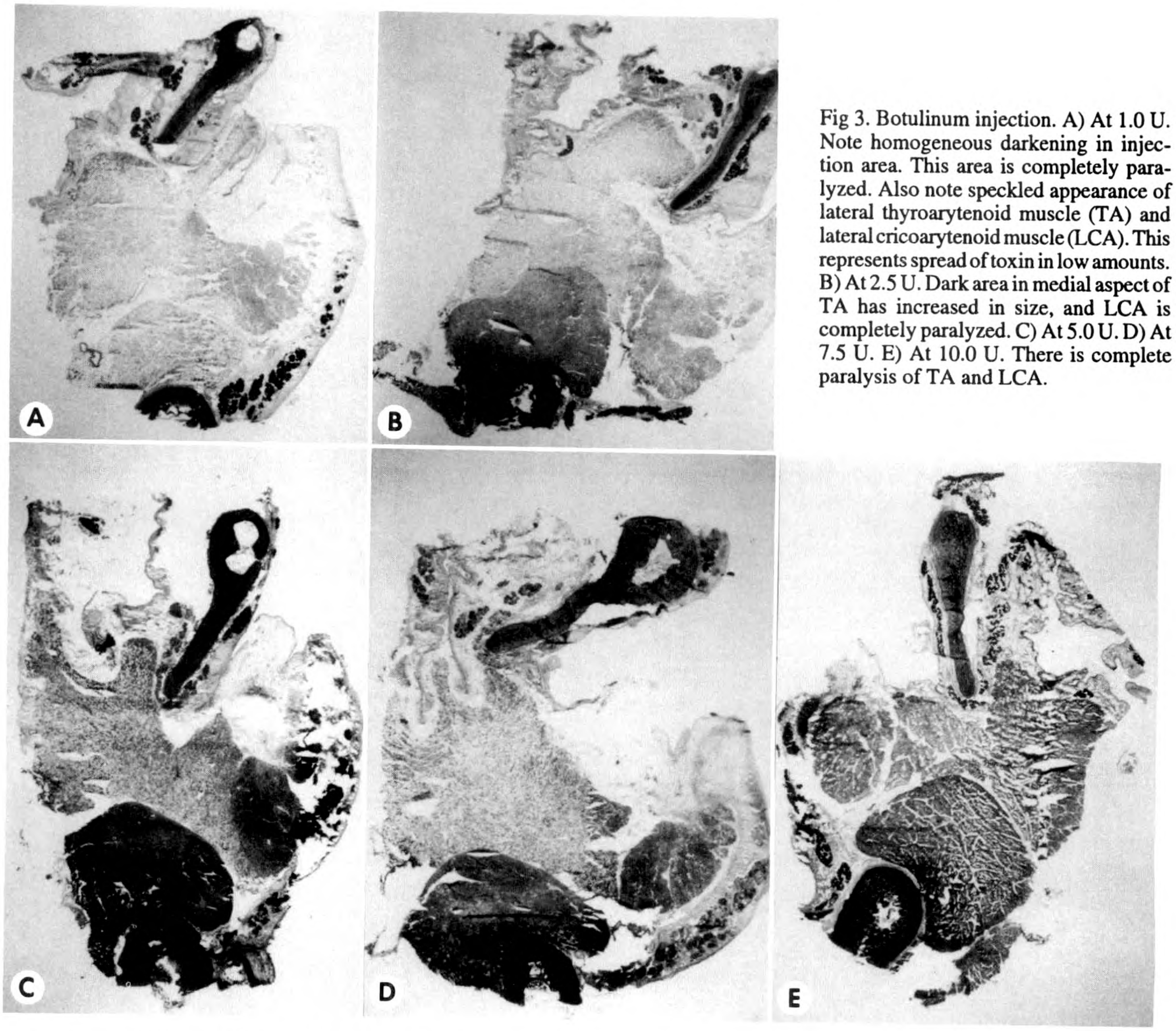

Fig 3. Botulinum injection. A) At 1.0 U. Note homogeneous darkening in injection area. This area is completely paralyzed. Also note speckled appearance of lateral thyroarytenoid muscle (TA) and lateral cricoarytenoid muscle (LCA). This represents spread of toxin in low amounts. B) At 2.5 U. Dark area in medial aspect of TA has increased in size, and LCA is completely paralyzed. C) At 5.0 U. D) At 7.5 U. E) At 10.0 U. There is complete paralysis of TA and LCA.

make it possible to increase the length of time between injections.

MATERIALS AND METHODS

Twelve mongrel dogs, each weighing approximately 18 to 22 kg, were used. All dogs were anesthetized with 65 mg/kg of phenobarbital and placed supine with a speculum inserted into the mouth. The vocal cords were visualized directly by using a fiberoptic light source. The lyophilized toxin (Oculinum) was stored at –20°C and was reconstituted with 0.9% saline prior to use.

Two separate operations were performed over a 24-hour period. In the first, either a 25- or 250-μL syringe (Hamilton Co) was used to inject the toxin directly into the TA muscle via the oropharynx. The injection was made 1.5 mm deep (until the bevel of the needle could no longer be seen through the vocal cord), 1.5 mm anterior to the vocal process and 0.5 mm lateral to the vocal cord edge. The amounts of the injections were 0.5, 1.0, 1.5, 2.5, 4.0, 5.0, 7.5, 10.0, and 12.5 U. Both TA muscles of each dog were injected with a different amount of toxin in order to minimize the number of dogs used. After 24 hours to allow the toxin to bind, the dog was reanesthetized. The recurrent laryngeal nerve was isolated and stimulated at 5 mA and 20 Hz for 20 minutes by means of a biphasic electrode nerve stimulator. A total laryngectomy was performed immediately after cessation of stimulation, and the dog was then killed painlessly with an overdose of phenobarbital. The excised larynges were immediately frozen in liquid nitrogen after removal. Anterior, midbelly, and posterior sagittal sections of 10-μm thickness were obtained in the TA muscle with a cryostat (Reichert-Jung Cryocut, Germany). The sections were mounted on chrome aluminum slides and stained for glycogen using PAS (Sigma Chemical Co, St Louis, Mo). Sections were projected onto a digitized computer tablet (Zeiss

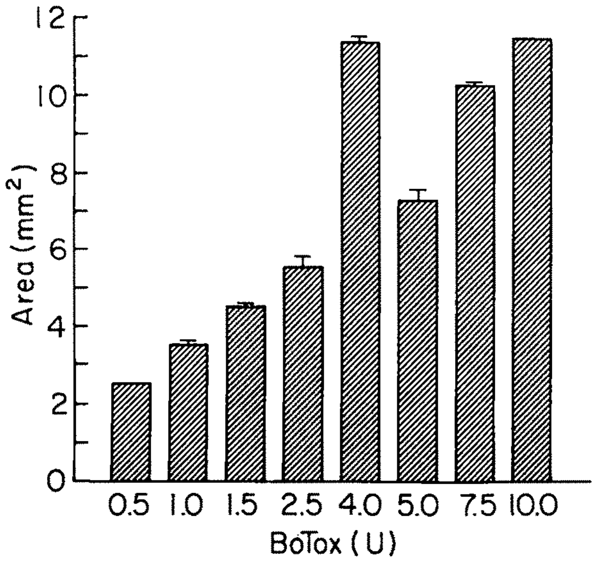

Fig 4. Graph of botulinum toxin dose versus paralyzed area. Error bars — SD.

Videoplan 2), and measurements of the area of the stained fibers were made.

Measurement of paralysis was made by examining the specimen via light microscopy. The magnified specimen was projected onto a background overlying the digitized computer tablet. The cross sections of individual muscle fibers were visible, and at 40x magnification the presence of glycogen was clearly determined. The area of each specimen was measured systematically. By using the homogeneous regions as one border, the outline of glycogen was followed. In regions in which the glycogen retention pattern became speckled, only 50% of the area of glycogen-filled fibers was used in the estimation of the area. There were two controls: an unstimulated noninjected muscle and a stimulated noninjected muscle.

RESULTS

The nonstimulated control had a homogeneous distribution of the dark glycogen-filled fibers (Figs 1 and 2A), while the stimulated control (Fig 2B) was completely depleted of glycogen and thus appeared pale.

Injections of botulinum toxin resulted in areas of glycogen retention providing evidence of chemical denervation. The different doses of botulinum toxin had different effects. At 0.5 U, there was no significant histologic evidence of paralysis at the injection site. The toxin seemed to spread diffusely throughout the muscle, as evidenced by the lightly speckled appearance of the fibers throughout the muscle. There was no area of localization of the toxin. The 1.0-U dose (Fig 3A) provided an area of localization in the TA muscle, and also diffused into the adjacent lateral cricoarytenoid (LCA) muscle, as evidenced by the speckling seen there. At the 2.5-U dose (Fig 3B) there was an increased area of glycogen retention throughout the TA mucle, in addition to increased diffusion to the LCA muscle. The fibers are more extensively involved, as speckling has been replaced by a more homogeneous pattern. At 5.0 U (Fig 3C) about 50% of the TA muscle has been affected by the toxin. There is a region of good localization in addition to the area affected by the spread of the toxin. The LCA muscle is also more heavily affected by the diffusion of the toxin. The same pattern is seen at 7.5 U (Fig 3D), except that there is a larger area of paralysis within the TA muscle, and the fibers in the LCA muscle are more darkly stained. Finally, at 10.0 U (Fig 3E) the toxin causes complete chemical denervation of the muscle. The speckled pattern has been replaced by a homogeneous pattern of glycogen retention that is identical to that seen in the nonstimulated control.

The area of glycogen retention in the TA muscle increased with the increasing dose of the toxin (Fig 4). There was a statistically significant positive correlation ($r = .808$; $p < .005$) between the dose of the toxin and the area of paralysis.

DISCUSSION

By using Botox in the current clinical range, our experiment provides histologic evidence of what has been seen clinically. Doses 10.0 U or larger not only completely diffuse throughout and denervate the TA muscle, but they spread to adjacent muscles such as the LCA muscle. Most likely this is the cause of the excessive weakness of the adduction muscles and the cases of aspiration and breathy weak phonation that have been documented clinically. Conversely, doses as low as 0.5 U may be unable to paralyze a sufficient number of muscle fibers to effect a paralysis that would be clinically significant. It is surprising that a dose as low as 1.0 U was able to diffuse to the LCA muscle. It has been postulated that the toxin receptor's binding capacity can be overcome at high doses of Botox, leading to diffusion and the side effects seen clinically, but our results, which showed spread at low doses, suggest that perhaps this may not be the only mechanism of spread. It is possible that our result could be explained by an inadvertent injection of the toxin very close to or into the fascia between the TA and the LCA muscles. Conversely, our previous study on the effects of fascia on the spread of Botox clearly showed that fascia only provided partial protection against diffusion of the toxin at low doses.[23] Therefore, it is equally possible that diffusion of the toxin out of the target muscle can occur at any dose.

Finally, there is a possibility that there exists some anatomic pathway that facilitates the diffusion of Botox to the LCA muscle. Further study needs to be done to elucidate the exact mechanism of diffusion for the toxin.

Although the results at the low dose range raise some questions, the results at the higher dose range corroborate the clinical judgment to avoid high doses in order to minimize unwanted side effects. It seems likely that multiple small doses placed in the center of the muscle have the best chance of avoiding side effects. Moreover, our results suggest that within the range of 1.25 to 7.5 U the effects of the toxin are clearly dose-related, while at doses above 7.5 U the toxin causes complete paralysis. Two specimens per dosage were used; it is therefore possible that the area of paralysis was either underestimated or perhaps overestimated. The reproducibility of findings at a particular dosage was good; however, the results would have been strengthened statistically with more specimens per dosage.

The peroral technique appears promising because it theoretically allows precise and reproducible positioning of the injection within the TA muscle. It is possible that the injection can be further localized if the external landmarks of the muscle motor end plate region can be identified. The applications of Botox are continuing to grow. Therefore, it is important to define the technique and site of injection to maximize the duration of its clinical effects.

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CONTINUOUS POSITIVE AIRWAY PRESSURE AS A PROMOTER OF LARYNGOSPASM DURING HALOTHANE ANESTHESIA

DAVID A. SILVA, MD
EL CERRITO, CALIFORNIA

IRA SANDERS, MD
NEW YORK, NEW YORK

Twenty mongrel dogs were anesthetized with halothane 2.0%, 1.25%, 0.94%, and 0.63% in oxygen. Thyroarytenoid (TA) and posterior cricoarytenoid (PCA) electromyography (EMG) tracings were recorded with the animal at rest, following mechanical irritation of the glottis, and during 20 mm Hg continuous positive airway pressure (CPAP) following either airway occlusion or hyperventilation. Adductor laryngospasm was defined as continuous tonic TA EMG activity, silent PCA EMG, and vocal cord adduction. Abductor laryngospasm was defined as continuous tonic PCA EMG activity, silent TA EMG, and vocal cord abduction. Combined laryngospasm was defined as continuous tonic PCA and TA EMG activity, with variable vocal cord position. The incidence of adductor laryngospasm following mechanical irritation was 30% to 50%. The combined incidence of laryngospasm during application of CPAP following airway occlusion or hyperventilation was 25% to 50%, and differed from the incidence of irritation-induced adductor laryngospasm by 5% or less at the same anesthetic level. Continuous positive airway pressure appears to be a stimulant of laryngeal muscle spasm comparable to mechanical irritation of the glottis.

KEY WORDS — abductor, adductor, anesthesia, continuous positive airway pressure, electromyography, halothane, laryngospasm, posterior cricoarytenoid muscle, thyroarytenoid muscle.

Previous work has reported that continuous positive airway pressure (CPAP) has promoted both adductor and abductor laryngospasm when preceded by either hyperventilation or airway occlusion in a dog model.[1,2] Direct mechanical stimulation of the glottis is associated with the occurrence of laryngospasm in lightly anesthetized patients.[3,4] In the current study, the incidence of CPAP-induced laryngospasm was compared to the incidence of laryngospasm induced by mechanical stimulation of the glottis.

METHODS AND MATERIALS

Twenty mongrel dogs, weighing between 18 and 24 kg, were studied. Anesthesia was induced with thiamylal sodium 15 mg/kg administered intravenously. The study animal was then placed in a supine position on an operating table. The mouth was opened and a size 8 double-cuffed endotracheal tube (ETT; Mallinckrodt, St Louis, Mo) was placed in the trachea under direct vision. This ETT has a cuff in the standard position, and a second cuff approximately 2 cm proximal to this. This second cuff was used to measure intraglottic pressure (IGP). The ETT was positioned with the second cuff at the level of the vocal cords and the first cuff in the trachea. The first cuff was inflated with air to prevent air leakage during lung inflation with 100% oxygen at 20 mm Hg CPAP. The IGP cuff was connected to a pressure transducer and inflated with air until the transducer demonstrated a tracing coincident with respiration. Anesthesia was maintained with the study animal spontaneously breathing 2.0% halothane in oxygen delivered at a 6-L/min flow rate through a standard adult anesthesia circuit. The mouth was stented open with a vaginal speculum. To allow an unobstructed view of the vocal cords, the epiglottis was percutaneously pinned to the thyrohyoid membrane. A strain gauge chest plethysmograph was placed to monitor respiratory excursions.

Hooked wire Teflon-coated stainless steel electromyography (EMG) electrodes were percutaneously placed in both thyroarytenoid (TA) muscles. Transmucosal posterior cricoarytenoid (PCA) muscle EMG electrodes were applied by using a custom-fitted latex electrode platform placed in the hypopharynx posterior to the larynx.[5] Electrode positioning and adequate EMG signal were confirmed during quiet spontaneous respiration. The chest plethysmograph, IGP ETT cuff transducer, and EMG output were displayed on an oscilloscope and printed on recording paper (Honeywell Medical Electronics, White Plains, NY).

Each animal was studied during the administration of four different levels of halothane (HAL) anesthe-

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From the Departments of Anesthesiology (Silva) and Otolaryngology (Sanders), Mount Sinai School of Medicine of the City University of New York, New York. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Mount Sinai School of Medicine.

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REPRINTS — Ira Sanders, MD, Dept of Otolaryngology, Box 1189, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

TABLE 1. INCIDENCE OF LARYNGOSPASM IN 20 ANIMALS (BY MUSCLE)

		2.0% Halothane		*1.25% Halothane*		*0.94% Halothane*		*0.63% Halothane*	
Maneuver	*Muscle*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
REST	None	0	0	0	0	0	0	0	0
IRRIT	TA	6	30	10	50	9	45	9	45
HV/CPAP	TA	5	25	8	40	7	35	7	35
	PCA	1	5	0	0	0	0	0	0
	BOTH	0	0	1	5	3	15	2	10
OCC/CPAP	PCA	2	10	4	20	8	40	6	30
	BOTH	3	15	5	25	1	5	2	10

See text for abbreviations.

sia: 0.63%, 0.94%, 1.25%, and 2.0%. Halothane was chosen for ease of maintenance of stable anesthetic levels, as opposed to the variability in plasma levels for parenterally administered anesthetics. The HAL levels were chosen to approximate minimum alveolar concentrations (MACs) for dogs of 0.67, 1.0, 1.33, and 2.1, respectively. (One MAC of an inhalational anesthetic produces immobility in 50% of subjects exposed to a noxious stimulus.[6]) We found HAL 0.63% allowed preservation of corneal reflexes while maintaining a quiescent animal. The PCA EMG, TA EMG, and vocal cord appearance were recorded under the following conditions at each HAL level.

1. REST (defined as quiet respiration).
2. Irritation (IRRIT; defined as five 1-cm ETT movements).
3. Hyperventilation (HV)/CPAP (defined as 10 500-mL positive pressure breaths delivered over 15 seconds followed by 20 mm Hg CPAP).
4. OCC/CPAP (defined as end expiratory airway occlusion for 50 to 60 seconds, followed by 20 mm Hg CPAP).

A 10-minute rest period was allowed between conditions 2 and 3, and between conditions 3 and 4. After condition 4, the HAL concentration was changed, and a 30-minute equilibration period followed. The animals used in this study were cared for in accordance with the standards for animal experimentation outlined by the National Institutes of Health.

RESULTS

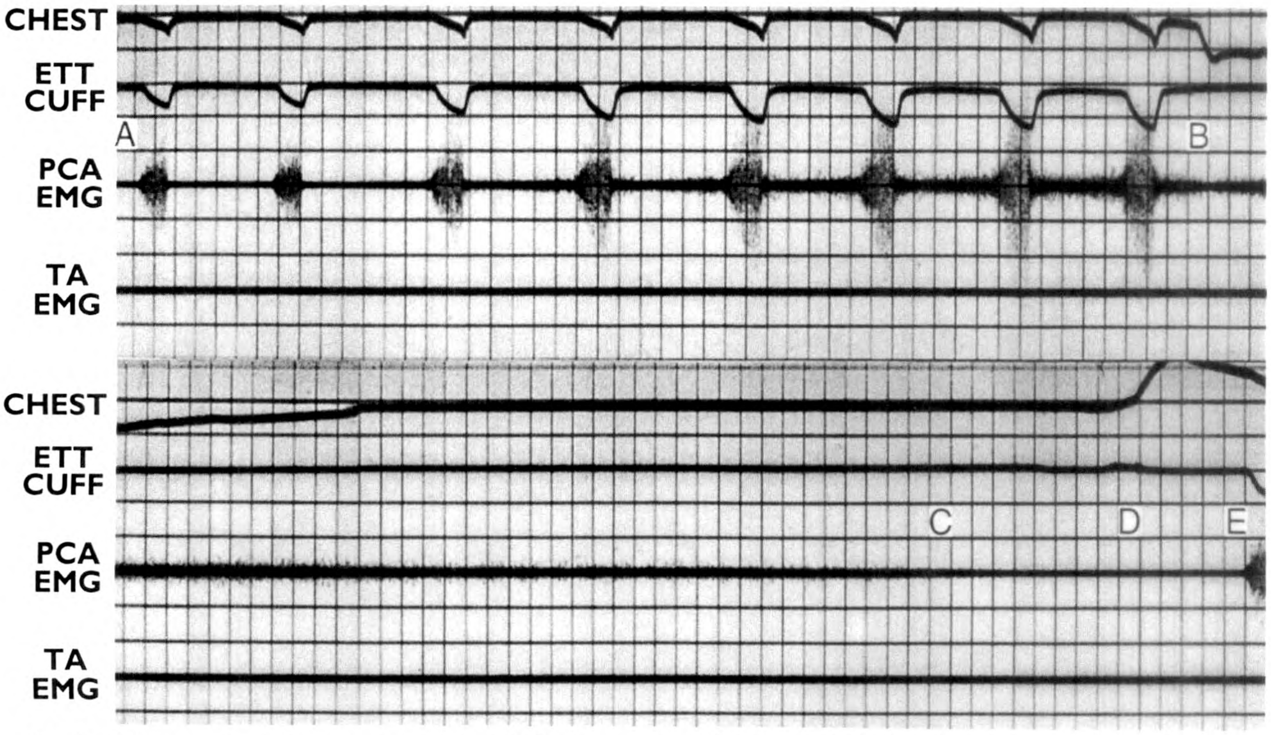
Adductor laryngospasm (TA spasm) was defined as continuous tonic TA EMG activity, silent PCA EMG, and vocal cord adduction. Abductor laryngospasm (PCA spasm) was defined as continuous tonic PCA EMG activity, silent TA EMG, and vocal cord abduction. Combined laryngospasm (BOTH) was defined as continuous tonic PCA and TA EMG activity, with variable vocal cord position. Unfortunately, the size of the IGP ETT cuff only allowed recording of extremes in vocal cord movement.

Quiet Breathing. The PCA EMG fired for 1 to 2 seconds at the start of inspiration, and the TA EMG fired for 1 to 2 seconds at the start of expiration with 0.63% to 1.25% HAL. At 2.0% HAL, the TA EMG was completely quiescent, while the PCA EMG fired for 1 to 2 seconds at the start of inspiration. There was no occurrence of PCA or TA spasm during quiet breathing (see REST in Table 1).

Mechanical Irritation of Larynx. There was no occurrence of PCA spasm following mechanical irritation of the larynx. Thyroarytenoid spasm occurred in 9 or 10 of the 20 study animals (45% to 50%) during 0.63% to 1.25% HAL, and in 6 of the 20 study animals (30%) with 2.0% HAL (see IRRIT in Table 1).

Hyperventilation Followed by CPAP. During application of CPAP, TA and PCA EMGs did not demonstrate phasic activity. Posterior cricoarytenoid spasm alone occurred in 1 of 20 (5%) study animals with 2.0% HAL. Thyroarytenoid spasm alone occurred in 7 or 8 of the 20 study animals (35% to 40%) with 0.63% to 1.25% HAL, and in 5 of the 20 study animals (25%) with 2.0% HAL. Spasm of both PCA and TA muscles (BOTH) occurred in 1 to 3 of the 20 study animals (5% to 15%) at 0.63% to 1.25% HAL (see HV/CPAP in Table 1).

Airway Occlusion Followed by CPAP. During application of CPAP, TA and PCA EMGs did not demonstrate phasic activity. Thyroarytenoid spasm alone did not occur following OCC/CPAP. Posterior cricoarytenoid spasm occurred in 6 to 8 of the 20 study animals (30% to 40%) with 0.63% and 0.94% HAL, 4 of the 20 (20%) with 1.25% HAL, and 2 of the 20 (10%) with 2.0% HAL. Spasm of both PCA and TA muscles (BOTH) occurred in 2 of the 20 study animals (10%) at 0.63% HAL, 1 of the 20 (5%) at 0.94% HAL, 5 of the 20 (25%) at 1.25% HAL, and 3 of the 20 (15%) at 2.0% HAL (see OCC/CPAP in Table 1). The Figure represents a sample tracing of OCC/CPAP at 2.0% HAL.



Graph of abductor, ie, posterior cricoarytenoid (PCA), spasm at 2.0% halothane. Vertical marks represent 1 second. A marks beginning of airway occlusion. Note increased intensity of phasic firing of PCA coincident with inspiration. B marks termination of occlusion and start of continuous positive airway pressure (CPAP). Note decrease in PCA signal 1 second after B, which then increases as CPAP is applied. C marks termination of PCA spasm. D marks end of CPAP. At E, spontaneous ventilation resumes. ETT — endotracheal tube, EMG — electromyography, TA — thyroarytenoid.

Table 2 summarizes the duration and incidence of laryngospasm for experimental conditions 2 through 4 at each anesthetic level. Note that at the same anesthetic level, the combined incidence of laryngospasm following CPAP differs from the incidence of irritation-induced adductor laryngospasm by 5% or less.

DISCUSSION

Clinically, while laryngospasm is recognized as an obstruction at the level of the glottis,[7] the pathophysiologic mechanism of laryngospasm in anesthetized humans is not clear. Fink[8] described laryngospasm as the closure of the supraglottic folds, the false vocal cords, and the true vocal cords. While Suzuki and Sasaki[9] differentiate between laryngospasm and the glottic closure reflex, Stone and Gal[3] consider laryngospasm to be the physiologic exaggeration of this reflex. The involvement of tonic or spastic contraction of intrinsic laryngeal muscles is likely.[9,10]

TABLE 2. DURATION AND INCIDENCE OF LARYNGOSPASM IN 20 ANIMALS

% Halothane	*Maneuver*	*Mean Duration ± SEM (s)*	*Animals*	
			No.	*%*
0.63	IRRIT	45.6 ± 6.2	9	45
	HV/CPAP	55.3 ± 6.5	9	45
	OCC/CPAP	57.9 ± 6.6	8	40
0.94	IRRIT	42.4 ± 6.3	9	45
	HV/CPAP	57.7 ± 8.3	10	50
	OCC/CPAP	67.8 ± 9.1	9	45
1.25	IRRIT	38.7 ± 5.8	10	50
	HV/CPAP	74.3 ± 23.1	9	45
	OCC/CPAP	57.3 ± 5.6	9	45
2.0	IRRIT	32.2 ± 8.1	6	30
	HV/CPAP	80.0 ± 13.1	6	30
	OCC/CPAP	55.8 ± 6.2	5	25

Includes all occurrences of TA and/or PCA spasm. See text for abbreviations.

Aviv et al defined an operational model of both adductor laryngospasm[1] and abductor laryngospasm[2] in the dog. This model required a very light barbiturate anesthetic, hyperventilation or airway occlusion, and application of 0.1 mol/L ammonia to the glottis followed by 40 mm Hg CPAP. The importance of the proper anesthetic level was stressed.[2] A sufficiently light anesthetic level, with preservation of corneal reflexes, was needed to allow the reproducible production of adductor and abductor laryngospasm.

We chose a similar dog model for the production of abductor and adductor laryngospasm. Simple mechanical irritation of the larynx produced TA spasm in 45% to 50% of study animals with 0.63% to 1.25% HAL and 30% of study animals with 2.0% HAL. The application of CPAP following either airway occlusion or hyperventilation produced TA spasm, PCA spasm, or combined TA and PCA spasm in 40% to 50% of study animals at 0.63% to 1.25% HAL and 25% to 30% at 2.0% HAL. It is not surprising that the occurrence of TA or PCA spasm is lowest at 2.0% HAL. Light anesthesia has been associated with laryngospasm,[3,4] and Baraka[11] reports that the treatment of laryngospasm following endotracheal extubation by the administration of intravenous lidocaine acutely deepens the anesthetic level.

Aviv et al[2] attributed the glottic response with lung inflation to carbon dioxide and oxygen levels following hyperventilation or airway occlusion. Laryngeal adductor activity has been described during lung inflation preceded by rapid ventilation,[12] and PCA activity is reported when lung inflation follows the administration of a hypercarbic hypoxic gas mixture to study animals.[13] This pattern is consistent with our finding of predominant TA spasm during HV/CPAP and PCA spasm with OCC/CPAP.

In a prior model, CPAP plus the glottic application of 0.1 mol/L ammonia was necessary to initiate adductor and abductor laryngospasm.[1,2] Although Rex[10] reported that laryngospasm can be triggered in the cat by the instillation of ether or HAL into the trachea, this does not seem to be a factor in dogs. There was no evidence of TA or PCA spasm during quiet breathing with administration of HAL in four different concentrations via an ETT. The decreased incidence of TA and PCA spasm at a 2.0% HAL concentration suggests that under these conditions a high concentration of HAL decreases the tendency toward sustained tonic activity of these muscles. In our subjects, CPAP itself was the inciting stimulus for the development of TA and PCA spasm.

The incidence of TA spasm, PCA spasm, or both during the administration of CPAP following either hyperventilation or airway occlusion was similar to the incidence of TA spasm following mechanical irritation of the glottis (Table 2). This finding held true for the four anesthetic levels tested, and implies that CPAP is as significant a stimulant to sustained spasm of laryngeal muscles as mechanical glottic irritation is to adductor muscle spasm.

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LARYNGOTRACHEAL RECONSTRUCTION IN ADULTS WITH THE STERNOCLEIDOMASTOID MYOPERIOSTEAL FLAP

MICHAEL FRIEDMAN, MD
CHICAGO, ILLINOIS

AMY D. MAYER, MD
NEW YORK, NEW YORK

Subglottic or tracheal reconstruction may be required in cases of subglottic stenosis, invasive thyroid carcinoma, or trauma. The sternocleidomastoid myoperiosteal flap uses clavicular periosteum on a muscle pedicle to provide vascularity. Clavicular periosteum is fibrous and durable and will conform to the shape of the trachea, forming bone to provide stability to the airway. The procedure is relatively simple and involves single-stage reconstruction. Success has been achieved in reconstruction of long-standing subglottic and/or tracheal stenosis and in cases of extreme tracheal defects. On the basis of 8 years' experience with this flap, we present the results from a series of 26 patients who underwent subglottic or tracheal reconstruction with the sternocleidomastoid myoperiosteal flap. Twenty-five of the 26 patients were successfully decannulated. Complications have been expanded to include one case of osteomyelitis of the sternum with mediastinitis, and 1 patient required revision. Subsequently, modifications of technique and patient management have been adopted. The complications compare favorably in frequency and in seriousness with those of other techniques for laryngotracheal reconstruction. We describe additional experience with this procedure and longer follow-up to establish its position as a first-line reconstructive approach for widespread clinical use.

KEY WORDS — invasive thyroid carcinoma, laryngotracheal reconstruction, myoperiosteal flap, sternocleidomastoid muscle, tracheal reconstruction, tracheal stenosis.

INTRODUCTION

Laryngotracheal reconstruction has proven to be one of the most challenging and controversial issues in otolaryngology today. Indications for reconstruction of the cricoid cartilage, subglottis, or trachea include subglottic stenosis, laryngeal trauma with tissue loss, and benign or malignant invasive thyroid carcinoma. The goal of laryngotracheal reconstruction is to provide a stable airway with preservation of normal phonation. To accomplish this, it is necessary to provide a durable, supportive framework over which endolaryngeal mucosa can regenerate. Preservation of laryngeal musculature and at least one recurrent laryngeal nerve is essential.

A variety of innovative techniques for subglottic reconstruction have been described and provide valuable surgical alternatives in the face of uncertain circumstances. A patient may have limited surgical options because of local tissue loss from previous unsuccessful attempts at laryngotracheal reconstruction or disfiguring neck trauma with destruction of cartilage. Some procedures are staged, requiring prolonged periods of time, and are technically difficult. Because there is no single universally applicable technique, it is necessary to become proficient in several and to realize the advantages and limitations of each procedure. Every case requires individual evaluation to determine which reconstructive procedure is most appropriate for the patient's particular disease process.

TABLE 1. PATIENT SEX AND AGE DISTRIBUTION AND TOTALS WITHIN FOUR PATIENT GROUPS

		Patient Groups			
Patient Characteristics	*Totals*	*Prolonged Endotracheal Intubation (Table 2)*	*Cricoid or Anterior Tracheal Defect (Table 3)*	*Invasive Thyroid Carcinoma (Table 4)*	*Trauma (Table 5)*
No. male/female	11*/16	4/6	1/2	1/8	5*/0
Total No. of procedures	27	10	3	9	5
Mean age	53.6	53.4	59.6	62.0	24.4
Age range	22-79	25-71	51-76	30-79	22-29
Average length of lesion (cm)	4.4	3.8	4.0	5.3	4.4

*One man had two reconstructive procedures.

From the Department of Otolaryngology and Bronchoesophagology, Rush Medical College of Rush University, Rush–Presbyterian–St Luke's Medical Center, and the Head and Neck Treatment Center, Illinois Masonic Medical Center, Chicago, Illinois (Friedman), and the University of the Health Sciences/Chicago Medical School, North Chicago, Illinois (Mayer).

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REPRINTS —Michael Friedman, MD, Dept of Otolaryngology and Bronchoesophagology, Rush–Presbyterian–St Luke's Medical Center, 1653 W Congress Pkwy, Chicago, IL 60612.

TABLE 2. PATIENT DATA IN CASES OF PROLONGED ENDOTRACHEAL INTUBATION

Pt	*Age*	*Sex*	*Condition Requiring Reconstruction*	*Length of Defect (cm)*	*Previous Treatment*	*Days to Stent or T-tube Removal*	*Days to Decannulation*	*Complications*	*Follow-up (mo)*
1	25	F	Subglottic and tracheal stenosis	6	Dilation	60, T-tube	74	Granulation tissue	12
2	58	M	Subglottic and tracheal stenosis	4		8	56	Aspiration of stent, wound infection	20
3	71	F	Subglottic and tracheal stenosis	4	Dilation, laser resection with keel placement, hyoid transposition	60	65		40
4	35	M	Subglottic and tracheal stenosis	4	Dilation	26	56		13
5	75	M	Subglottic and tracheal stenosis	3	Dilation	44	58		40
6	36	F	Glottic and subglottic stenosis	4		44	98	Wound infection, superior mediastinal abscess, osteomyelitis of clavicle and sternum	42
7	44	M	Subglottic and tracheal defect	5	Dilation 8x	56	70	Granulation tissue 2x	24
8	54	F	Subglottic and tracheal defect	3	Dilation 3x, laser 2x	42	84	Granulation tissue 2x	20
9	68	F	Glottic and subglottic defect	3	Laser 4x	35	49		6
10	68	F	Subglottic stenosis	2	Dilation 3x, laser 3x	42	56	Granulation tissue	12

The sternocleidomastoid myoperiosteal flap technique is suitable for extensive tracheal defects that may not be correctable by other techniques. On the basis of 8 years of experience, we present the results of 26 patients who underwent a total of 27 procedures for subglottic or tracheal reconstruction with the sternocleidomastoid myoperiosteal flap and review in detail all complications associated with the technique. We also describe modifications of the technique that have been introduced to minimize complications and improve versatility.

PATIENTS AND METHODS

The patients include only those with subglottic and tracheal stenosis or defects large enough to warrant open reconstruction. Patients with lesser degrees of defects or stenoses were treated with endoscopic dilation, laser ablation of scar tissue, or T-tube stenting without open reconstruction. Those who failed endoscopic management were treated with the sternocleidomastoid myoperiosteal flap.

Patients were divided into four categories requiring reconstruction (Table 1). Ten patients sustained prolonged endotracheal intubation (Table 2) with subsequent subglottic and tracheal stenosis (eight patients) or glottic and subglottic stenosis (two patients). Three patients developed an unstable airway following loss of the integrity of the cricoid arch from high tracheostomy (Table 3). Nine patients had invasion of the larynx and trachea from thyroid carcinoma (Table 4). Four patients sustained trauma to the laryngotracheal complex, including three patients with gunshot wounds to the subglottic and tracheal region, and one patient who suffered from a crush injury of the larynx and trachea following a motor vehicle accident (Table 5). For Tables 1 through 5, it is assumed that a classic stent was used unless a T-tube is specified.

Computed tomographic or magnetic resonance scans were performed to evaluate the location, length, and diameter of the stenotic segment or defect. Figures 1 and 2 illustrate the extent of involvement and the postoperative results.

TABLE 3. PATIENT DATA IN CASES OF CRICOID OR ANTERIOR TRACHEAL DEFECT

Pt	*Age*	*Sex*	*Condition Requiring Reconstruction*	*Length of Defect (cm)*	*Previous Treatment*	*Days to Stent or T-tube Removal*	*Days to Decannulation*	*Complications*	*Follow-up (mo)*
11	76	F	Unstable airway	3		42	56		36
12	51	F	Unstable airway	4		42	56		13
13	52	M	Subglottic and tracheal defect, unstable airway	5	Dilation 4x, T-tube for 6 mo	42	56		18

In these cases, anterior cricoid arch was inadvertently removed during tracheostomy.

RESULTS

Overall, the 27 reconstructive procedures evaluated in this review were performed on 16 women and 10 men, between 1984 and 1991 (Table 1). The average age was 53.6 with a range of 22 to 79 years. Twenty-one patients required some form of stenting, including 16 regular stents and five T-tubes. T-tubes were used in three cases of invasive thyroid carcinoma, one case of prolonged endotracheal intubation, and one case of trauma to the neck. All cases of reconstruction for prolonged endotracheal intubation and for unstable airway required stenting, while only four of nine cases of invasive thyroid carcinoma, and four of five cases of trauma required stenting of the airway. The mean length of time for stent or T-tube placement in 21 patients was 50 days (range, 8 to 96 days). The mean length of time from stent or T-tube removal to decannulation in 21 patients was 35.4 days (range, 5 to 217 days). The mean length of time from reconstruction to decannulation in 26 procedures (one patient was not decannulated; Table 5, patient 23) was 68.1 days (range, 7 to 313 days).

Table 2 summarizes a group of patients who had glottic, subglottic, or tracheal stenosis following prolonged endotracheal intubation. A majority of patients had a history of previous attempts for treatment of their stenoses, including dilation and laser resection of scar tissue. One patient (patient 3) underwent standard dilation, laser vaporization of scar tissue with keel placement, and eventual hyoid flap reconstruction, without decannulation until she underwent successful reconstruction with the sternocleidomas-

TABLE 4. PATIENT DATA IN CASES OF INVASIVE THYROID CARCINOMA

Pt	*Age*	*Sex*	*Condition Requiring Reconstruction*	*Length of Defect (cm)*	*Previous Treatment*	*Days to Stent or T-tube Removal*	*Days to Decannulation*	*Complications*	*Follow-up (mo)*
14	68	F	Cricoid and first two tracheal rings	4	Multiple thyroid procedures		21		7
15	76	F	Tracheal rings 1-4	4			18		18
16	71	F	Cricoid and tracheal rings 1-6, 60% circumference	5.5	Multiple thyroid procedures	56, T-tube	180	Granulation tissue 5x	13
17	76	F	Cricoid and tracheal rings 1-4	5	Thyroid procedure	56	70	Granulation tissue 5x	12
18	64	F	Cricoid and first tracheal ring	2			14		17
19	79	M	Cricoid and tracheal rings 1-4, 60% circumference	6		42, T-tube	56	Partial flap necrosis, breakdown of suture line with drainage	5
20	30	F	Subglottic and tracheal defect	6	Thyroid procedure	50, T-tube	68	Granulation tissue	54
21	36	F	Subglottic defect	3			7		53
22	58	F	Subglottic defect	2			7		76

TABLE 5. PATIENT DATA IN CASES OF TRAUMA

Pt	*Age*	*Sex*	*Condition Requiring Reconstruction*	*Length of Defect (cm)*	*Cause*	*Previous Treatment*	*Days to Stent or T-tube Removal*	*Days to Decannulation*	*Complications*	*Follow-up (mo)*
23	29	M	Subglottic defect	3	Gunshot wound to neck		Unknown	Tracheostomy-dependent	Wound infection, breakdown of suture line	*
24	22	M	Subglottic and tracheal defect	5	Gunshot wound to neck		42	58		26
25	24	M	Cricoid and four tracheal rings	6	Gunshot wound to neck		42, T-tube	60		9
26	23	M	Crush injury of larynx and trachea	4	Motor vehicle accident		42	64	Restenosis	30
	24		Restenosis following decannulation after elective tracheostomy for cranioplasty		Tracheostomy following decannulation		96	313	Breathy voice	30

*Followed up for 2 days before transfer to spinal cord unit at another institution.

toid myoperiosteal flap. Nine of 10 patients required stent placement, and 1 patient required T-tube placement because of the 6-cm length of the lesion (patient 1). Patient 6 required a prolonged period of time before decannulation because of procedure-related complications.

Table 3 lists three patients who developed unstable airways after inadvertent destruction of the anterior cricoid arch following high tracheostomy. All three patients required 6 weeks of stent placement and 2 weeks between stent removal and decannulation, for a total of 8 weeks' time from reconstruction to decannulation.

Table 4 lists nine patients with laryngeal and tracheal invasion of thyroid carcinoma. None of the patients underwent previous reconstructive procedures on their airway, although four patients underwent previous thyroid procedures. One patient required stent placement, and three others required T-tube placement. T-tubes were used for the most extensive lesions. Five patients did not require any form of stenting. Patient 3 required a prolonged period before decannulation because of recurrent granulation tissue formation at the site of reconstruction.

Table 5 summarizes four patients who sustained trauma to the larynx and trachea, including one patient (patient 26) who is listed twice because he underwent two sternocleidomastoid myoperiosteal flap reconstructive procedures on two separate occasions. All four of the patients were treated acutely. Each of the five procedures involved some form of stent placement, including four procedures requiring regular stents and one procedure with T-tube placement, again, because of the extent of the lesion. Patient 23 was unavailable for follow-up, and the time of stent removal was unknown. Patient 26 underwent a second reconstruction and will be discussed in Complications.

Table 6 summarizes data from Tables 2 through 5 pertaining to the procedure time frame, including time from reconstruction to stent or T-tube removal, time from removal to decannulation, and total time from reconstruction to decannulation. Although patient groups are not large enough to draw statistically significant conclusions, in general, patients with invasive thyroid carcinoma or trauma experienced a longer procedure time frame, possibly reflecting the severity of their laryngotracheal defects. A general comparison of procedure time frame can also be made among patients who underwent reconstruction with a standard classic stent, a T-tube, or no stent. Patients with stents or T-tubes had a similar time course, while patients not requiring any form of airway stenting had a shorter time course.

COMPLICATIONS

Table 7 is an evaluation of procedure-related complications encountered, including type of complication, number of patients, number of occurrences, treatment used, possible etiologic factors, and suggested modifications of technique. There were a total of 16 instances of complications among the 27 procedures performed.

Granulation tissue formation during the immediate postoperative period was the most frequent com-

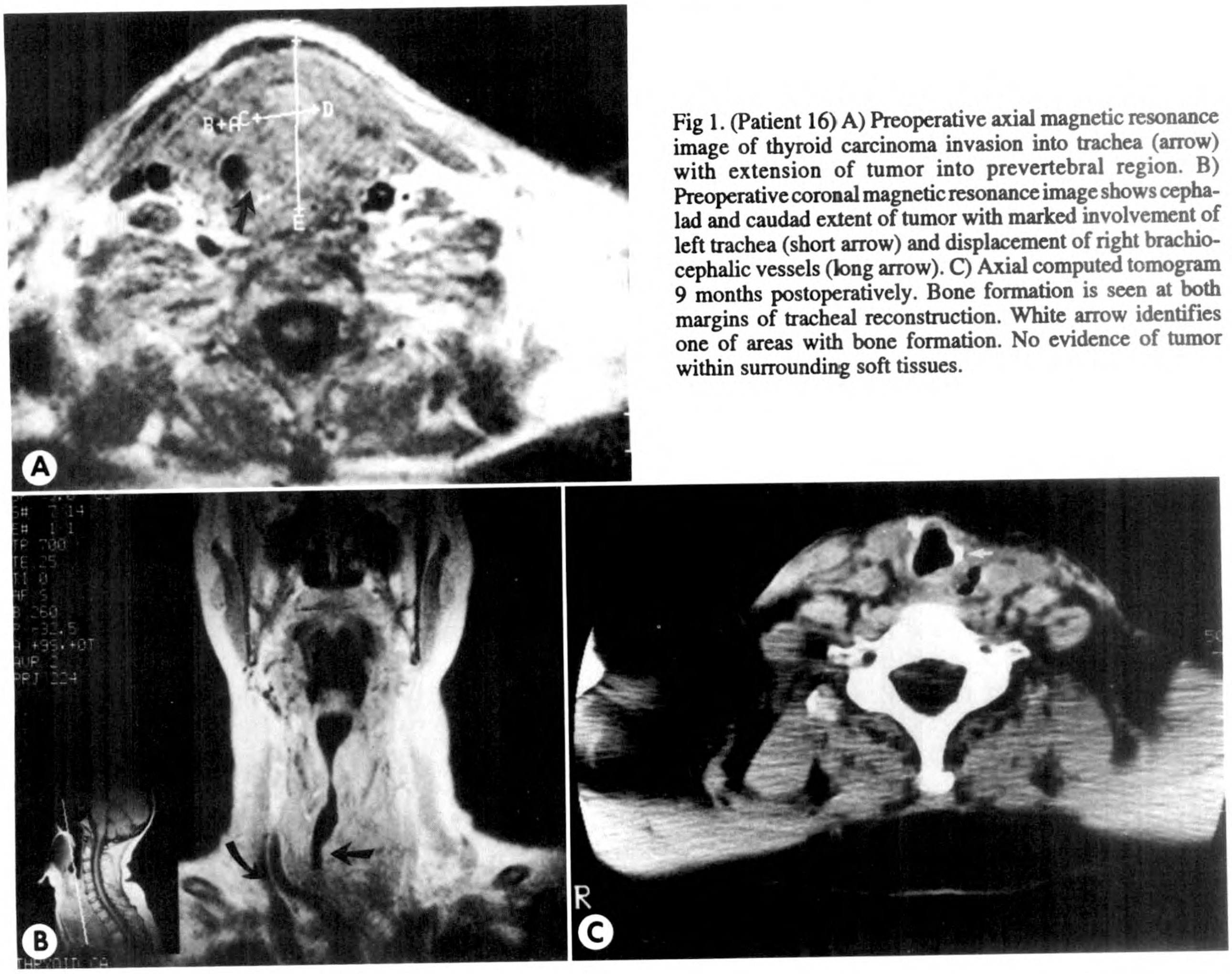

Fig 1. (Patient 16) A) Preoperative axial magnetic resonance image of thyroid carcinoma invasion into trachea (arrow) with extension of tumor into prevertebral region. B) Preoperative coronal magnetic resonance image shows cephalad and caudad extent of tumor with marked involvement of left trachea (short arrow) and displacement of right brachiocephalic vessels (long arrow). C) Axial computed tomogram 9 months postoperatively. Bone formation is seen at both margins of tracheal reconstruction. White arrow identifies one of areas with bone formation. No evidence of tumor within surrounding soft tissues.

plication, occurring in seven patients and often occurring multiple times in the same patient. In all cases, the granulation tissue was removed endoscopically (manually or with the laser), and patients were observed for recurrence. These patients often required a prolonged period before decannulation. Granulation tissue at the site of reconstruction is likely due to the fact that the sternocleidomastoid myoperiosteal flap is unepithelialized. Secondary intention healing with mucosal migration for reepithelialization of the luminal surface of the flap is required, even with large mucosal defects. This requirement has made granulation tissue a fairly common complication. With large defects, granulation tissue formation should be considered an adverse result of the surgical procedure rather than a complication. The ideal reconstruc-

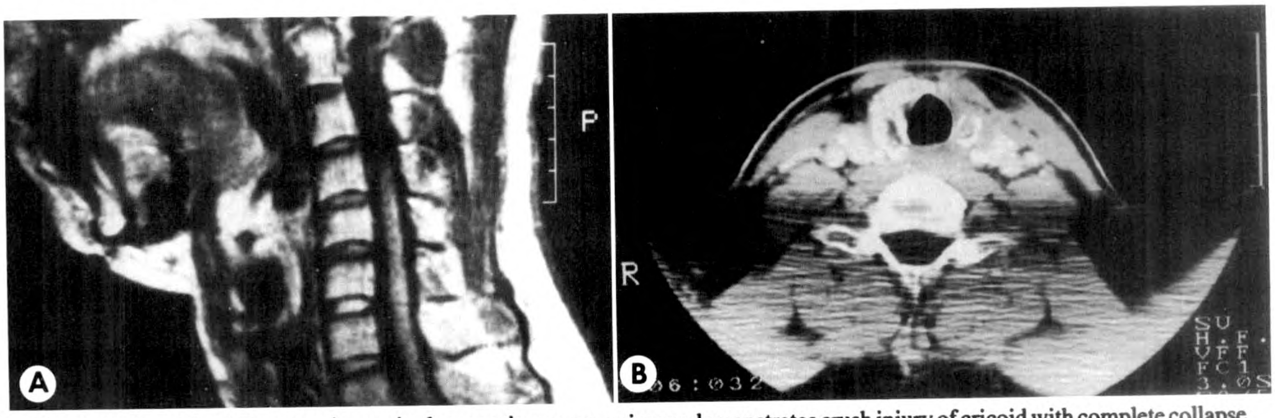

Fig 2. (Patient 26) A) Preoperative sagittal magnetic resonance image demonstrates crush injury of cricoid with complete collapse of upper airway. B) Axial computed tomogram 12 months after second reconstructive procedure. Healed calcified sternocleidomastoid myoperiosteal flap forming contour of trachea is evident.

TABLE 6. COMPARISON OF PROCEDURE TIME FRAME AMONG FOUR PATIENT GROUPS AND AMONG PATIENTS REQUIRING STENTS, T-TUBES, AND NO STENT

	Days Before Removal of Stent or T-tube		*Days From Stent or T-tube Removal to Decannulation*		*Days From Reconstruction to Decannulation*	
Patient Group	*Average**	*Range*	*Average**	*Range*	*Average**	*Range*
Prolonged endotracheal intubation (Table 2)	41.7 (10)	8-60	24.9 (10)	5-54	66.6 (10)	49-98
Cricoid anterior tracheal defect (Table 3)	42 (3)	42	14 (3)	14	56(3)	56
Invasive thyroid carcinoma (Table 4)	51 (4)	42-56	45 (4)	14-124	49 (9)	7-180
Trauma (Table 5)	74 (4)	42-96	68.3 (4)	16-217	123.8 (4)	58-313
Total procedures	50 (21)	8-96	35.4 (21)	5-217	70.8 (25)	7-313
Stents	44.9 (16)	8-60	34.1 (16)	5-217	79.1 (16)	7-313
T-tubes	50.0 (5)	42-60	40.4 (5)	14-124	87.6 (5)	56-180
No stent					13.4 (5)	7-21

*Numbers in parentheses represent total procedures used to calculate value.

tion would use an epithelialized flap. Theoretically, the sternocleidomastoid myoperiosteal flap could be combined with a split-thickness skin graft or a mucosal graft to provide for an epithelialized surface. The split-thickness skin graft or mucosal graft can be sutured to the clavicular periosteum prior to the final positioning of the reconstructive flap,[1] or the stent or T-tube can be ensheathed by a split-thickness skin graft before placement in the airway.

Wound infection occurred in three cases, with resolution of two cases with intravenous antibiotics and local wound care. The third case (Table 2, patient 6) was a patient with poorly controlled insulin-dependent diabetes who sustained a diabetic coma with subsequent tracheostomy dependency for 5 years that necessitated sternocleidomastoid myoperiosteal flap reconstruction. Following reconstruction, she had a wound infection on postoperative day 23 and was treated with intravenous antibiotics and local wound care. By day 44, the patient had a mediastinal abscess and osteomyelitis of the clavicle and sternum in the region of flap harvest, requiring incision, drainage, and debridement. A second debridement procedure was performed on day 68, and the patient was eventually decannulated on day 98 without further evidence of infection. A breach in sterile technique must be considered as a possible etiologic factor in all three cases of wound infection. The patient with the abscess and osteomyelitis may have been at an increased risk for infection because of her diabetes and because of removal of the sternal periosteum. In subsequent procedures, the sternal head of the sternocleidomastoid muscle has been transected, but its periosteum is left attached to the sternum, with only the clavicular head of the muscle used for reconstructive purposes. Earlier and more aggressive debridement of the infected bone might have prevented the need for a second procedure.

One patient (Table 2, patient 2) aspirated the stent into his left main stem bronchus 8 days after reconstruction. Emergency bronchoscopy was performed to retrieve the stent. The airway was stable, and no stent was reinserted. This particular patient was one of the first in this series. All stents since have been carefully secured in place with heavier wire sutures and skin buttons, without further occurrence of stent aspiration. Wire sutures placed through a Montgomery stent can easily tear through the stent if placed near the ends of the stent.

Partial flap necrosis occurred in one patient (Table 4, patient 19) who underwent selective neck dissection of lymph node levels IV and VI for thyroid carcinoma. In this case, the ipsilateral sternocleidomastoid muscle was used for reconstruction. Possibly the blood supply to the muscle was compromised, leading to some flap necrosis. The area of necrosis resolved with adequate airway. In the future, the use of the contralateral sternocleidomastoid muscle may be indicated when any kind of neck dissection is performed.

A more severe episode of flap necrosis occurred in a trauma patient (Table 5, patient 23). This case involved a gunshot wound with an automatic weapon that damaged the larynx, trachea, esophagus, and cervical spine, leaving the patient quadriplegic. The esophageal injury was closed at the same time that the tracheal injury was reconstructed. A leak in the esophageal closure resulted in abscess formation in the neck and mediastinum. Exploration of the neck

TABLE 7. COMPLICATIONS

Type	*No. of Pts*	*No. of Occurrences*	*Treatment*	*Results*	*Possible Causes*	*Possible Modifications*
Granulation tissue	7	15	Endoscopic removal, manual or laser	Resolved	Unepithelialized flaps	Mucosal or split-thickness skin grafts
Wound infection	3	3	Intravenous antibiotics, local wound care	Resolved in two patients, abscess formation and osteomyelitis in one	Exposed sternum and clavicle, possible breach in sterile technique	Leave muscle and periosteum on sternum, meticulous sterile technique
Osteomyelitis	1	1	Intravenous antibiotics, two surgical procedures for incision and drainage	Resolved	Exposed sternum and clavicle, possible breach in sterile technique	Leave muscle and periosteum on sternum, meticulous sterile technique, early debridement of infected bone
Stent aspiration	1	1	Endoscopic removal	Resolved	Poorly secured stent	Wire securement with skin buttons
Partial flap necrosis	1	1	Local care	Resolved, healed with adequate airway	Patient had selective neck dissection of lymph node levels IV and VI, compromised blood supply to lateral SCM	Use contralateral SCM if neck dissection is done
Flap necrosis (esophageal leak, mediastinal abscess)	1	1	Incise and drain abscess	Tracheostomy-dependent	Esophageal leak secondary to esophageal trauma	Patient lost to follow-up, drainage of mediastinum in face of esophageal leak
Restenosis	1	1	Secondary reconstruction with SCM MP flap	Second decannulation at 313 days	Tracheostomy for elective cranioplasty 1 mo after decannulation	Avoid tracheostomy during early post-decannulation period
Breathy voice	1	1	None		Vocal cord paralysis or glottic injury	Possible Teflon injection

SCM — sternocleidomastoid muscle, MP — myoperiosteal.

revealed a viable periosteal flap that had broken down at the inferior aspect of the reconstruction. After the reconstruction, the patient was transferred to a regional spinal cord injury unit at another institution, and no attempt to repair the subglottic airway was undertaken, so the patient remained tracheostomy-dependent. The patient was eventually lost to follow-up. Perhaps the esophagus could have been repaired with a contralateral sternocleidomastoid muscle flap instead of primary closure.[2]

A second sternocleidomastoid myoperiosteal flap reconstruction was performed on one patient (Table 5, patient 26). This patient successfully underwent laryngotracheal reconstruction, with stent removal and decannulation occurring within 64 days. An elective frontal cranioplasty was performed within 1 month of decannulation. At the time of this procedure, the patient underwent elective tracheostomy in order to avoid intubation. Unfortunately, secondary decannulation was not tolerated, and the patient required a second reconstruction with prolonged stent removal (96 days) and decannulation at 313 days. Reintubation and tracheostomy should be avoided, if possible, in the early decannulation period. Bone growth continues for months after stent removal and decannulation.[3] After two reconstructions, this patient maintains a breathy voice, most likely due to traumatic disruption of a recurrent laryngeal nerve, although inadvertent iatrogenic causes cannot be ruled out. The patient had complete collapse of his airway with no voice prior to initiation of treatment.

MODIFICATIONS

During the past 8 years, since the first sternocleidomastoid myoperiosteal flap procedure was performed by the senior author (M. F.), subtle modifications of the technique have evolved based on attempts to minimize or eliminate complications that were encoun-

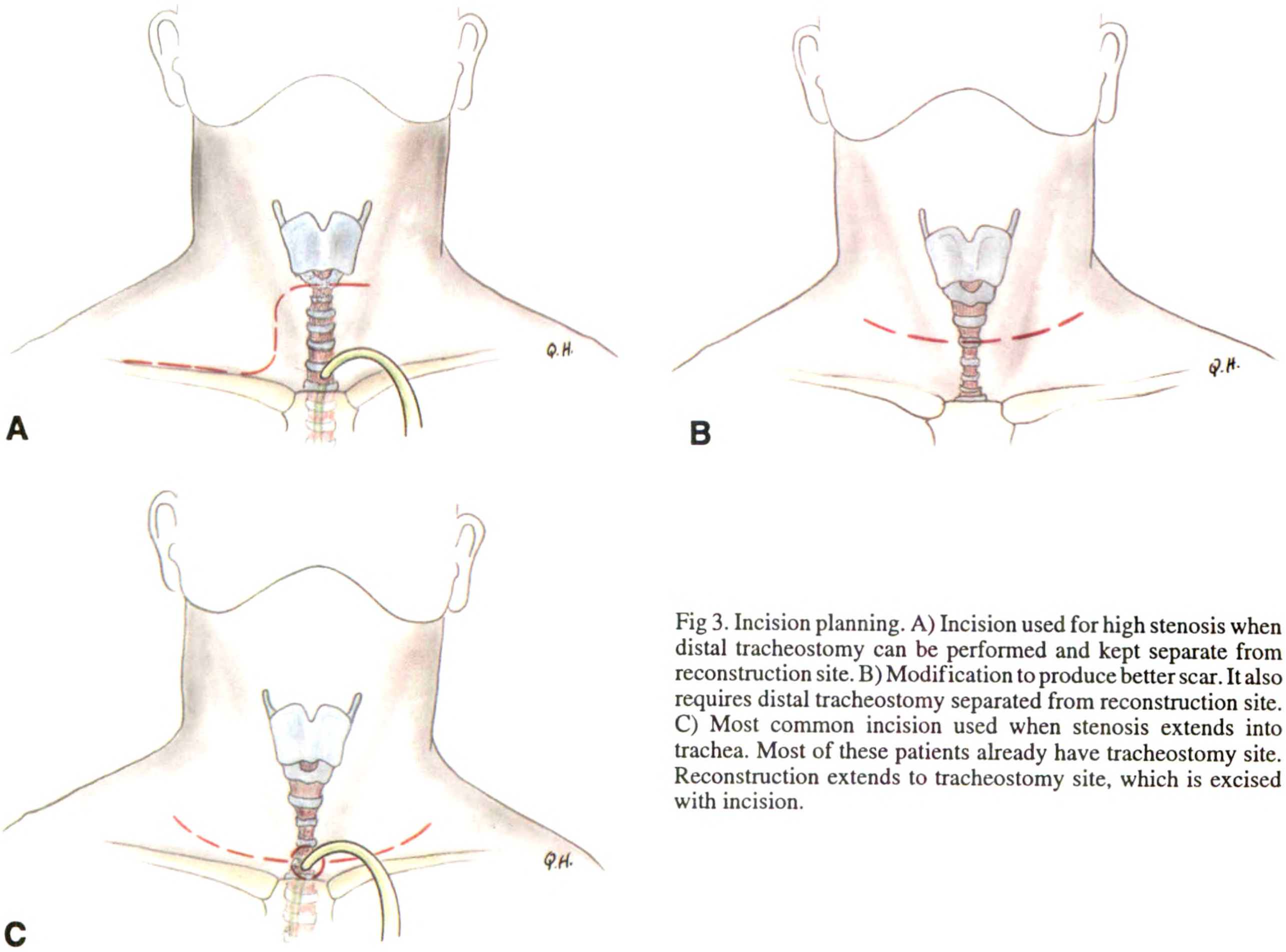

Fig 3. Incision planning. A) Incision used for high stenosis when distal tracheostomy can be performed and kept separate from reconstruction site. B) Modification to produce better scar. It also requires distal tracheostomy separated from reconstruction site. C) Most common incision used when stenosis extends into trachea. Most of these patients already have tracheostomy site. Reconstruction extends to tracheostomy site, which is excised with incision.

tered. Some modifications are the result of increased experience with the procedure.

Although the initial procedures were performed with either a horizontal skin incision or an S-shaped incision, it has become clear that there are certain indications for each one.

In patients with a long neck and high trachea or subglottic defects, a distal tracheostomy can be performed with at least three healthy tracheal rings between the reconstruction site and the tracheostomy site. In such cases, the flaps should be designed so that the donor and reconstruction areas are separated from the new tracheostomy site. The S-shaped incision is ideal. The majority of cases, however, involve reconstruction of all of the trachea that can be exposed through the neck, and a distal tracheostomy is not feasible. In such cases, T-tubes are used at the distal area of reconstruction. In such cases a horizontal incision allows ideal exposure (Figs 3-5).

The second modification deals with transection of the sternal head of the sternocleidomastoid muscle. Since the periosteum of the sternum is difficult to dissect and small in surface area, it is not useful for reconstruction. The periosteum is therefore not elevated off the bone, but left intact. The intact periosteum should protect the sternum from osteomyelitis, which occurred in one of our early cases in which the periosteum was removed. The sternal head of the muscle is transected 2 to 3 cm above the sternum to allow rotation of the flap and use of the clavicular periosteum for reconstruction. The third modification involves coverage of the clavicle with the pectoralis muscle. The muscle is loosely approximated to fascia to cover denuded bone.

The use of T-tubes or stents has also changed over the years. The advantages of each are discussed in the section that follows. In general, T-tubes are used much more frequently now, because they allow the patient to breathe and speak relatively normally with a plugged tube immediately after surgery. Their use requires, however, a great deal of experience on the part of the surgeon and nursing staff to avoid T-tube complications.

STENTS

Over the past 8 years, indications for stenting have also evolved to include the following recommendations: defects greater than 30% of the circumference of the cricoid require a stent or T-tube; tracheal

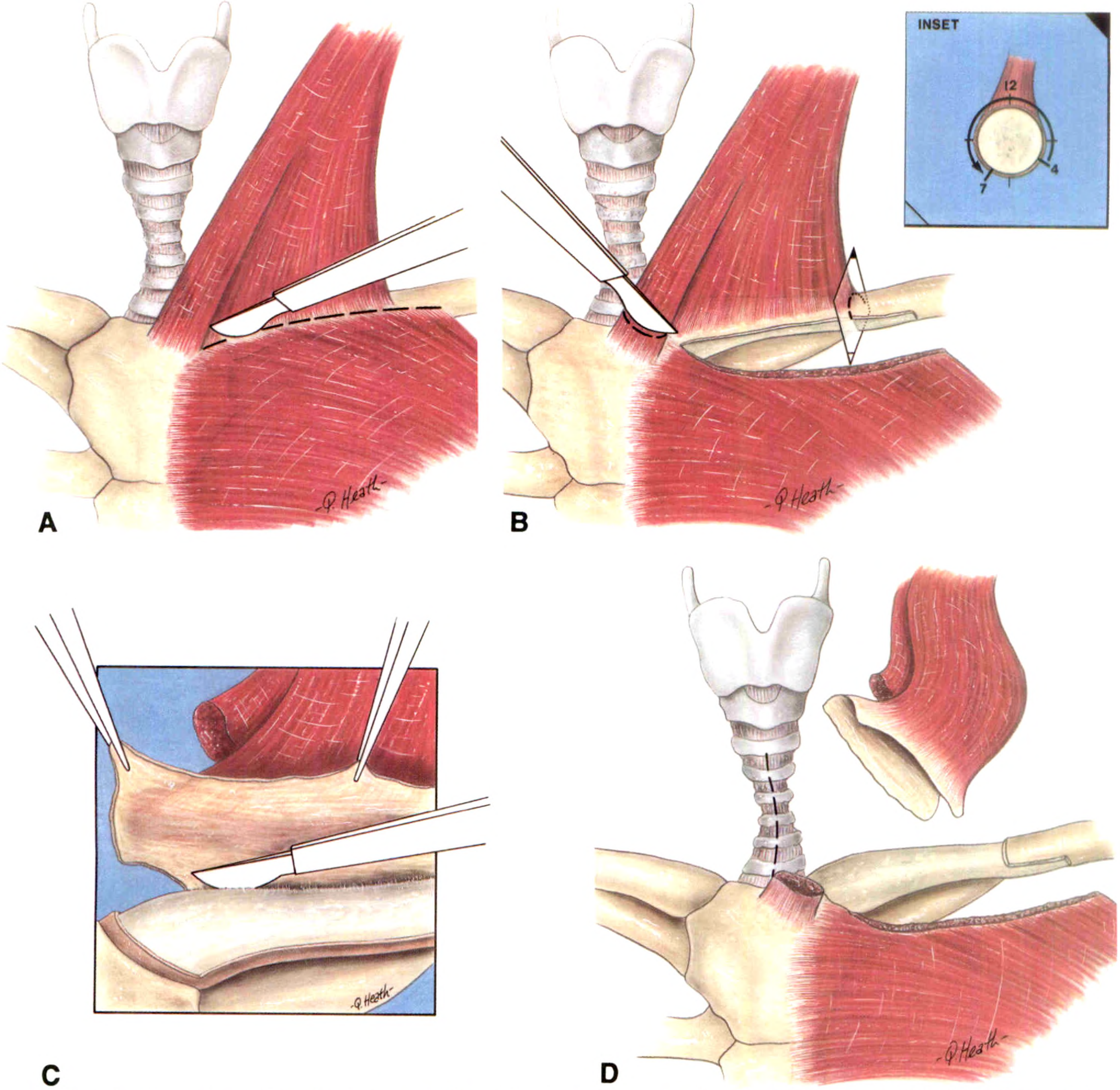

Fig 4. Incision and elevation of periosteum. A) Pectoralis muscle is cut away from clavicle to expose clavicular periosteum. B) Sternal head of sternocleidomastoid muscle is transected, leaving periosteum intact on sternum. Clavicular periosteum is incised and elevated. Inset) Degree of periosteum elevation. C) After elevation of periosteum, posterior cut is made from inner surface. D) Trachea (and cricoid if necessary) is opened. No tissue is excised.

defects even greater than 30% of the circumference may not require stenting unless they involve more than 3 cm of length; and tracheal defects greater than 6 cm require a T-tube. All patients with prolonged endotracheal intubation, an unstable airway, or a large defect from invasive thyroid carcinoma or trauma received a stent or a T-tube. In patients with glottic involvement, a Montgomery preformed stent was used. For patients with subglottic and tracheal defects, a foam-filled homemade rubber glove stent was used.

Absolute indications for T-tube use as both a stent and a tracheostomy include patients who cannot undergo the usual tracheostomy tube placement (two to three rings below the subglottic defect) because of technical difficulties created by the presence of the sternum. A relative indication for T-tube placement can occur in any case of laryngotracheal reconstruction. Early patients in this series received more stents than T-tubes, but now more T-tubes are used. T-tubes are interchangeable with stents, assuming a distal tracheostomy can be created.

Stents and T-tubes each have specific advantages and disadvantages (Table 8), and all factors must be

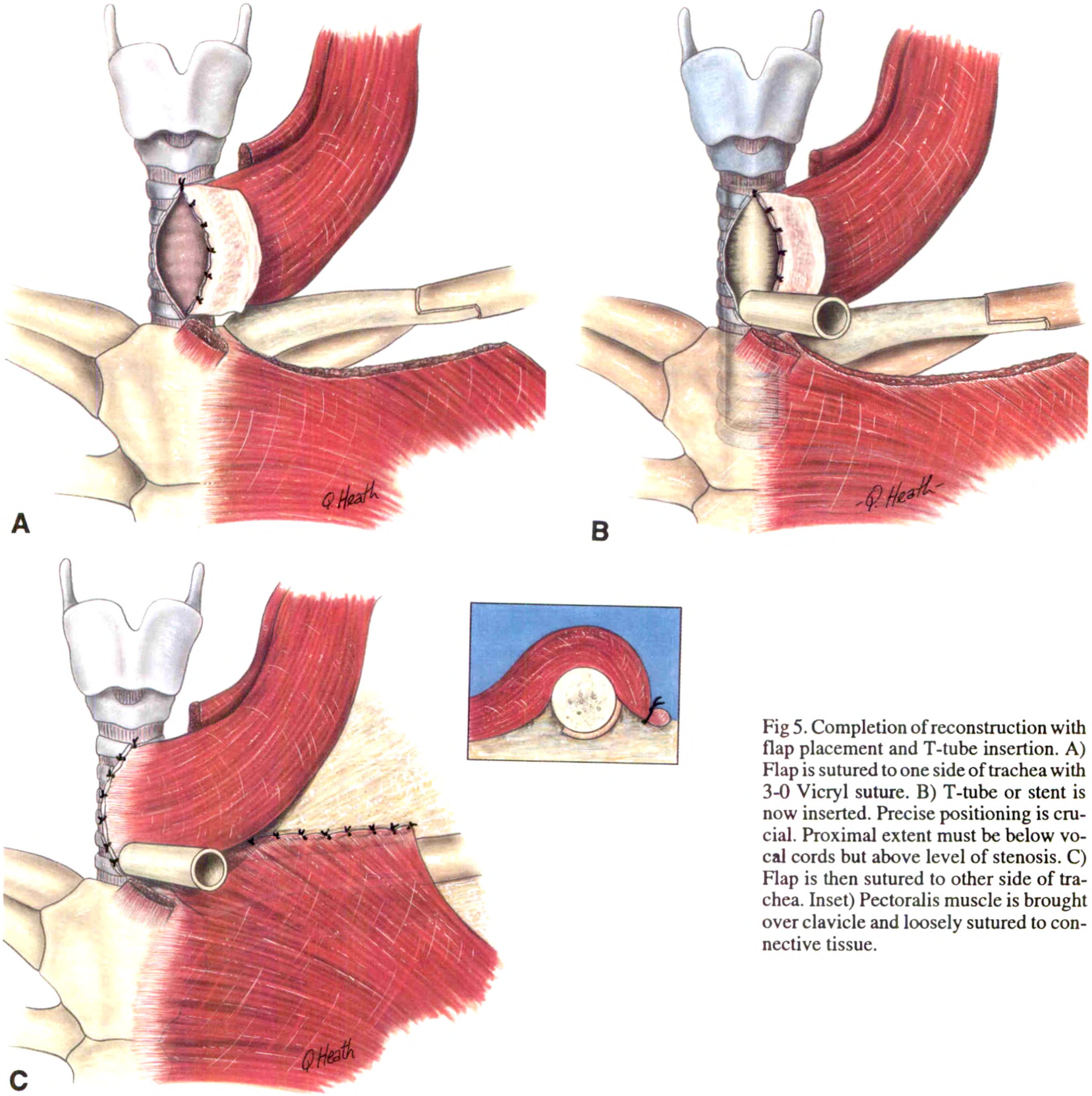

Fig 5. Completion of reconstruction with flap placement and T-tube insertion. A) Flap is sutured to one side of trachea with 3-0 Vicryl suture. B) T-tube or stent is now inserted. Precise positioning is crucial. Proximal extent must be below vocal cords but above level of stenosis. C) Flap is then sutured to other side of trachea. Inset) Pectoralis muscle is brought over clavicle and loosely sutured to connective tissue.

weighed before deciding which type of stent to use. Generally, stents are easier to use and to manage postoperatively, but the patient cannot speak, and constant humidification of the airway is required. Stents must be carefully secured in place to avoid aspiration. T-tubes allow for normal speech and airway humidification and are self-securing, but a good deal of familiarity and experience is required to achieve precise cutting and fitting of the device. Aspiration will occur if the T-tube is cephalad to the vocal cords. Placement must be above the reconstruction site and below the vocal cords. It is also very important to have knowledgeable nursing staff who understand the mechanics of a T-tube and know how to properly apply suction both cephalic and caudal to the stoma to avoid mucous plugging and obstruction. When the upper limb of the T-tube gets plugged or when the upper limb hits the undersurface of the cord, complications such as obstruction, no speech, and vocal cord trauma occur. If the T-tube lies above the cords, the patient cannot speak and is at risk for aspiration. Low placement causes incomplete stenting with subsequent restenosis. The T-tube is also difficult to change. Because it is not placed within a rigid framework, the potential exists for movement of the T-tube with healing. Accurate placement at surgery does not guarantee that the position will be maintained over the estimated 6-week period.

Trauma patients with multiple injuries often re-

TABLE 8. STENT VERSUS T-TUBE USE WITH STERNOCLEIDOMASTOID MYOPERIOSTEAL FLAP

Procedure	*Advantages*	*Disadvantages*
Stent*	• Easier to fit • Routine tracheostomy care • Easy to change tracheostomy if obstruction occurs • Sealed system allows ventilatory support	• No speech • Tracheostomy-dependent • Requires humidification • Wire securement
T-tube	• Allows speech • Normal humidification • Self-securing	• Precise cutting and fitting above reconstruction and below vocal cords • Difficulty with subglottic reconstruction (easier with tracheal) • Requires nursing familiarity • Obstruction risk • Air leak does not permit respiratory support • Aspiration if T-tube is cephalad to vocal cords

*For those patients with glottic and subglottic stenosis, Montgomery preformed stent was used. For patients with subglottic and tracheal defects, foam-filled homemade stent was used.

quire prolonged ventilation and continuous positive airway pressure. T-tubes cannot provide a sealed system and are therefore not recommended in these patients. A stent and a tracheostomy tube are preferable.

DISCUSSION

Procedures designed for the repair of laryngotracheal defects are varied, but share the common goal of providing a stable airway with preservation of normal phonation. Deciding on the proper procedure for reconstruction depends on the extent and location of the lesions and the surgeon's preference. It is not uncommon for some options to be used up by previous reconstruction attempts, trauma that disrupts the strap muscle, or previous surgery of other kinds. A balance between the risk of the procedure and the severity of the disease must be considered as well.

Optimal reconstruction of the laryngotracheal complex addresses or includes the following considerations:

1. The use of pliable material.
2. The use of fibrous and elastic material for creation of an airtight seal and a tension-free suture line.
3. The use of rigid material for prevention of airway collapse.
4. The use of vascularized material to minimize the possibility of flap necrosis or resorption and subsequent contraction.
5. Epithelialization of the intraluminal surface.
6. A single-stage procedure.
7. One surgical field, to reduce the risk of infection and trauma to the patient.
8. A reproducible procedure that can be performed with relative technical ease by any qualified head and neck surgeon.

The sternocleidomastoid myoperiosteal flap procedure satisfies seven of the eight criteria listed above, lacking an intraluminal epithelialized surface.

Other procedures for laryngotracheal reconstruction include repeated dilation or laser vaporization of soft tissue stenoses, the microtrapdoor technique[4,5] using the carbon dioxide laser, primary thyrotracheal anastomosis,[6,7] prosthetic interpositional or segmental grafts,[8-12] the composite graft technique[13] using an autologous mucosal cyst and cortical bone, other autologous grafts such as nasal septum or epiglottis,[14-18] the sternohyoid myocutaneous rotary door flap,[19,20] and the hyoid transposition flap.[21,22] Each procedure meets some of the criteria for an optimal flap, although no one procedure satisfies all the criteria.

All of the procedures have been reported to be successful by their proponents, with variable complication rates. Complications include leakage around the suture line, infection, scar formation with restenosis, hemorrhage from erosion of grafts into adjacent vessels, flap necrosis, and others.

CONCLUSIONS

Although multiple techniques for laryngotracheal reconstruction are available, all have limitations. It is necessary to be knowledgeable about several techniques. Experience with the sternocleidomastoid myoperiosteal flap[23-26] has affirmed its use for major defects including large segments of trachea. Most large defects require either a classic stent or a T-tube, as discussed. The flap is available for secondary procedures after its own failure and after other procedure failure (eg, after hyoid transposition failure). Theoretically, it can be used after any other kind of procedure, assuming that the sternocleidomastoid muscle is intact. It cannot be used after radical or modified neck dissection. The sternocleidomastoid myoperiosteal flap satisfies most of the criteria for an optimal flap, with good long-term results. Complications that have been encountered have led to modifications in an attempt to decrease morbidity.

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DETECTION OF REGULATORY FACTORS OF LYMPHOKINE-ACTIVATED KILLER CELL ACTIVITY IN HEAD AND NECK CANCER PATIENTS TREATED WITH INTERLEUKIN-2 AND INTERFERON ALPHA

GARY L. CLAYMAN, DDS, MD GREGORY YOUNG, MD DOROTHY L. TAYLOR, MS
HOWARD E. SAVAGE, PHD PIERRE LAVEDAN, MD STIMSON P. SCHANTZ, MD
HOUSTON, TEXAS

Interleukin-2 (IL-2) and interferon-α (INF-α) are biologic modifiers that have met with limited clinical success in the treatment of human malignancies. We conducted a phase 2 trial of IL-2–IFN-α in patients with advanced or unresectable squamous cell carcinoma of the upper aerodigestive tract. Two patients were analyzed sequentially for serum induction phase–blocking factors of lymphokine-activated killer (LAK) cell activity in their therapy. Serum also modulated LAK activity independent of autologous or allogeneic effector cells. Significantly inhibitory serum samples were stable in multiple freezings and thawings. Heat-treating the inhibitory serum, at 56°C for 30 minutes, only partially removed the serum inhibitory capacity. Sequential analysis of p55 and p75, subunits of IL-2 receptors, showed that absence of effector cell lytic activity was associated with markedly decreased fluorescence of the IL-2Rp75 subunit only. No significant alteration of the IL-2Rp55 subunit occurred with therapy. These studies support the theory that lymphocyte and multiple serum factors, developing during IL-2–IFN-α therapy, regulate the induction of in vitro LAK activity. Further understanding of these factors may lead to improvements in biologic modifier therapy.

KEY WORDS — biologic modifiers, interferon-α, interleukin-2, interleukin-2 receptor, lymphokine-activated killer cell.

INTRODUCTION

Serologic factors that block the induction of lymphokine-activated killer (LAK) cells remain to be identified. To date, the unidentified inhibitory induction factors have been demonstrated to act in a dose-dependent fashion,[1-4] and their inhibition can be reversed by high recombinant interleukin-2 (rIL-2) doses. The presence of these induction phase–blocking factors was demonstrated by Itoh et al[1] in patients with metastatic melanoma, but was not seen in patients with only primary disease or in patients used as controls. Serologic inhibition of the induction phase was also seen, to a variable degree, in all patients with squamous cell carcinoma of the head and neck.[4] The inhibitory mechanisms of these in vitro serologic factors and their relationship to the limited clinical response, in instances in which biologic response modifiers are used, remain to be established.

Interleukin-2 (IL-2) may function as a growth- or differentiation-stimulating agent for various hemopoietic cells, including T cells,[5,6] B cells,[7,8] natural killer (NK) cells,[9,10] and monocytes.[11,12] These effects are mediated by the high-affinity or intermediate-affinity IL-2 receptor, but not by the low-affinity receptor. The high-affinity receptor is proposed to be a complex of at least two different subunits: IL-2Rp55 (p55) and IL-2Rp75 (p75), the intermediate-affinity receptor of only the p75 unit, and the low-affinity receptor of only the p55 unit.[13-17] Following the development of a mouse monoclonal antibody (MAb) named TU27 MAb, specific for human p75,[18] we analyzed the expression of the p75 and p55 receptors in patients receiving continuous intravenous infusion rIL-2 and intramuscular interferon-α (IFN-α) immunotherapy. Additionally, the relationship between receptor expression and in vitro cytotoxic potential and induction cytotoxic capacity was investigated. The results demonstrate that serologic factors modulate LAK induction independently of IL-2Rp75 and IL-2Rp55 expression.

MATERIALS AND METHODS

Populations Studied. The two patients studied in a phase 2 trial of IL-2–IFN-α had squamous cell carcinoma of the upper aerodigestive tract confirmed by biopsy. The tumors of both patients were considered nonresectable. Neither patient had been previously treated with biologic response modifiers; both, however, had received radiotherapy, the last treatment occurring at least 4 months prior to the initiation of rIL-2–IFN-α therapy.

Patient 1 was a 68-year-old man with locally

From the Department of Head and Neck Surgery, University of Texas M. D. Anderson Cancer Center, Houston, Texas. Supported in part by Cancer Center Support (Core) Grant CA-16672.

REPRINTS — Gary L. Clayman, DDS, MD, Dept of Head and Neck Surgery, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 69, Houston TX 77030.

recurring laryngeal squamous cell carcinoma. Patient 2 was a 46-year-old woman with regional and distant recurrent laryngeal squamous cell carcinoma. Patients signed consent forms approved by the Surveillance Committee of the University of Texas M. D. Anderson Cancer Center. Lymphocyte values and cytotoxicity standards were based on those of six healthy, nonsmoking individuals (four men and two women) ranging from 24 to 57 years old.

Study Design. Patients were treated with rIL-2 given by continuous intravenous infusion at a dose of 3.0×10^6 U/m^2 per day on days 1 through 4, 8 through 11, and 15 through 18. Each 18-day treatment constituted one cycle. Interferon-α was administered intramuscularly at a dose of 5×10^6 U/m^2 per day each day that rIL-2 was given. Cycles were repeated following a 2-week rest, depending on the absence of disease progression and of significant toxicity.

Peripheral Blood Lymphocyte Preparation. Peripheral blood lymphocytes (PBLs) were harvested as previously described by Bugis et al.[4] Monocytes were removed from the mononuclear cell suspension by their characteristic adherence to plastic. Recovered lymphocytes were stored overnight at 4°C. Viability of cell fractions following storage was greater than 95% as determined by trypan blue exclusion. Lymphocytes for receptor analysis were fresh-frozen and stored in liquid nitrogen for simultaneous staining and analysis.

A gibbon monkey lymphocyte cell line, MLA144, was maintained in RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and used as a positive control for the p75 IL-2 receptor.

Treatment of Serum. Samples of serum were drawn synchronously with PBLs. The samples to be used within 24 hours were stored overnight at 4°C. The remaining serum samples were divided into aliquots and stored at –70°C. Heat-inactivated serum experiments were performed by heating serum at 56°C for 30 minutes.

Biologic Agents. Recombinant IL-2 and IFN-α were both provided by Hoffmann-LaRoche (Nutley, NJ). The National Cancer Institute Biological Response Modifiers Program standard specific activity of IL-2 was 1.5×10^7 U/mg protein. The specific activity of IFN-α was 2×10^8 U/mg protein. All systemic infusions of IL-2 were performed through central venous catheters.

LAK Activation. Recombinant IL-2 was added at a concentration of 10 U/mL to PBLs at a concentration of 1×10^6 cells per milliliter, in 24-well plates. The PBLs were incubated at 37°C in 5% carbon dioxide for 6 days (previously determined as the optimum period), recovered, and resuspended in complete medium (CM). Recovery after incubation averaged 80% (range, 65% to 100%).

Target Cells. K-562 cells, an established myeloid tumor cell line that is both NK- and LAK-sensitive, were cultured with RPMI 1640 supplemented with 10% FCS. MDA-686-Ln, a squamous cell carcinoma cell line resistant to NK but sensitive to LAK cells,[19] was maintained in Dulbecco's modified Eagle's medium (DMEM) with nutrient mixture Ham's F-12 with 10% FCS. On the day of labeling, 2×10^6 target cells were labeled with 100 mCi radioactive sodium chromate (sodium [^{51}Cr]chromate, specific activity 500 Ci/mg, Amersham, Arlington Heights, Ill) for 1.5 hours in a total volume of 300 µL. The 1×10^3 target cells were assessed for total uptake of chromium on a gamma counter (Packard Instruments, Downers Grove, Ill; results, 5,000 to 7,000 cpm). Maximum release of target cells was determined by adding 50 µL of target cell preparation to 150 µL of Triton X-100 and allowing the mixture to sit for 4 hours at room temperature prior to harvesting.

Cytotoxicity Assay. A standard 4-hour ^{51}Cr-release assay was used to test cytotoxicity, as previously described by Schantz et al.[20] Effector-target ratios from 6:1 to 25:1 were achieved in triplicate in flat-bottomed microtiter wells. Dose-response induction experiments using autologous serum (AS) concentrations from 6.25% to 50% were implemented at effector-target ratios of 12:1. Dose-response experiments using FCS and control serum solutions from 6.25% to 50% were carried out to analyze serum effects. Following a 4-hour incubation, 100-µL aliquots were removed from each well, and their release of ^{51}Cr was counted on a gamma spectrometer (Packard Instruments). Cytotoxicity expressed as a percentage was determined with the following formula:

$$\% \text{ Cytotoxicity} = [(\text{Experimental cpm} - \text{Spontaneous cpm})/(\text{Maximum cpm} - \text{Spontaneous cpm})] \times 100$$

Spontaneous release of ^{51}Cr, measured by incubation of target cells with RPMI 1640 with 10% FCS (or DMEM F12 with 10% FCS) for 4 hours, was routinely 5% to 9% for K-562 and 10% to 14% for MDA-686-Ln.

As in prior studies,[20] induction-phase modulation of the LAK phenomenon was calculated as follows:

$$\% \text{ Induction Inhibition} = [(\% \text{ Cytotoxicity in CM [Induction]} - \% \text{ Cytotoxicity in AS [Induction]})/\% \text{ Cytotoxicity in CM [Induction]}] \times 100\%$$

Immunophenotypic Labeling and Analysis. Thawed PBLs were labeled with MAbs according to the manufacturer's specifications for flow cytometric analysis.

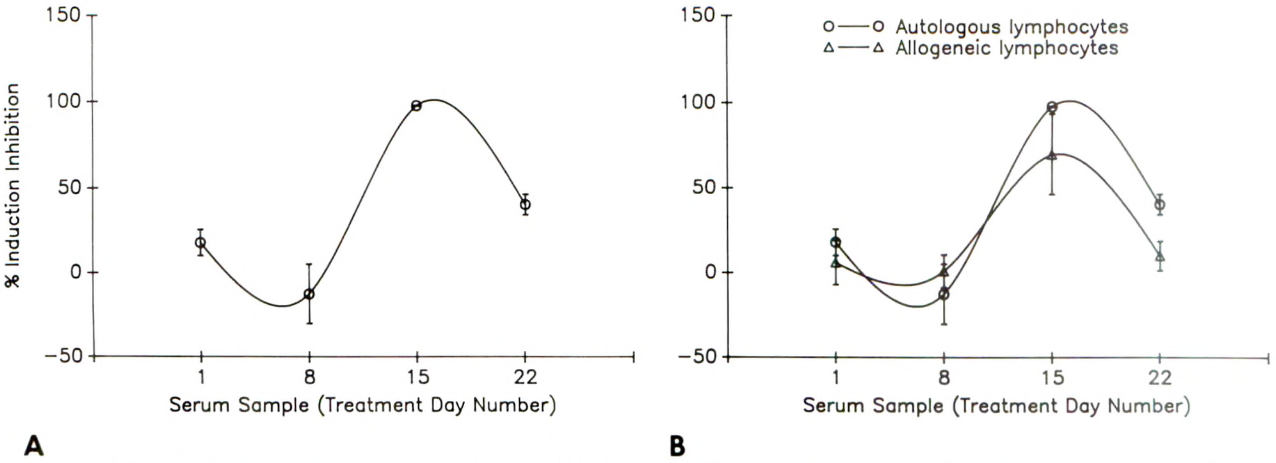

Fig 1. (Patient 1) Percentage of induction inhibition (at 25:1 effector-target ratio) produced by serum samples at cycle 1 of therapy. A) With four autologous lymphocyte samples obtained at 1-week intervals during second cycle of therapy. Included are autologous results also obtained at time of therapy (cycle 1). B) With four samples of allogeneic lymphocytes from noncancer controls and two from cancer patients.

Statistics. Serum inhibition was analyzed by using a paired *t* test. Pearson's correlation was used to determine the relationship between induction inhibition and receptor expression.

Monoclonal Antibodies. Mouse MAbs used were TU27 MAb (IgG1) specific for human IL-2Rp75[18] and phycoerythrin (PE)–conjugated CD25 (Becton Dickinson Monoclonal Center, Mountain View, Calif) specific for IL-2Rp55. Noncancer control lymphocytes and MLA 144 were used as positive receptor controls.[21] Receptors were stained for single-color and two-color fluorescence analysis. Isotype-matched fluorescein isothiocyanate (FITC) and streptavidin PE-conjugated antibodies were used as controls to exclude Fc-related binding; all procedures were performed at 4°C. Indirect staining strategy was used for the p75 receptor with goat anti mouse IgG. Briefly, primary staining of lymphocytes with TU27 MAb was performed at 4°C. Secondary staining with biotinylated goat anti mouse reagent and subsequent labeling with streptavidin PE (Becton Dickinson, Sunnyvale, Calif) were performed. Nonspecific binding was blocked with excess IgG1 (Cappel Laboratories, Cochranville, Pa, and Cooper Biomedical, Malvern, Pa). The cells were then washed twice, fixed, and stored at 4°C in the dark until analyzed. Labeled cells were filtered for debris through nylon mesh. Analysis was performed by FACScan flow cytometry (Becton Dickinson Immunocytometry Systems, Mountain View, Calif). On the basis of the characteristic forward- and wide-angle light scatter patterns, electric gates were set on the lymphocytes.

RESULTS

Autologous Serum LAK Induction Experiments. Ten percent AS was added to PBLs harvested from a patient during IL-2–IFN-α therapy, as follows. Weekly serum samples and lymphocyte cultures were obtained from patients during IL-2–IFN-α therapy. Serum samples were stored at −70°C on days 1, 8, 15, and 22 (day 1 = pretreatment) and were then tested for induction modulation on lymphocytes from days 36, 43, 50, and 57. These results were then compared with those previously obtained from lymphocytes from days 1, 8, 15, and 22 (Fig 1A). Induction inhibition was reproducible on autologous lymphocytes. No alteration in induction inhibition was noted when fresh samples stored at 4°C were compared with those stored at −70°C (data not shown). Repeated thawing (maximum number of thaws performed was four) and refreezing to −70°C did not alter serum induction inhibition (data not shown).

Allogeneic Serum LAK Induction Experiments. The PBLs of two patients with head and neck cancer and four control noncancer patients were activated in the identical 10% allogeneic serum as previously employed. Although the nascent CM induction capability of lymphocytes varied among individuals, the induction modulation of 10% serum, independent of the lymphocyte source (Fig 1B), appeared similar.

In addition, markedly inhibitory serum (>75% inhibition) produced significantly reduced viability of harvested activated cells in both autologous and allogeneic systems, as compared with CM LAK standards ($p < .001$).

Heat-Induced Changes in Induction Modulation. Serum samples stored at −70°C were thawed to 4°C and used in parallel induction experiments in autologous and allogeneic systems. In addition, parallel experiments used thawed serum specimens heated to 56°C for 30 minutes (Table 1). Inhibitory serum samples were significantly reversed by heat inactiva-

TABLE 1. CYTOTOXIC ACTIVITY OF 10 U/mL INTERLEUKIN-2–ACTIVATED PERIPHERAL BLOOD LYMPHOCYTES INDUCED WITH KNOWN INHIBITORY SERUM AND HEAT-INACTIVATED SERUM

		*% Cytotoxicity**					
	Subject No.	*Of CM LAK*	*Of Serum LAK†*	*Of AS LAK*	*Of Heat-Inactivated Serum LAK†*	*Of Heat-Inactivated AS LAK*	*% Change§*
Controls	1	27	5		22		63
	2	65	3		50		72
	3	67	40		61		31
	4	38	14		26		32
Cancer patients	1	39		10		24	36
	2	38		13		22	23
	1	68		4		52	70

Peripheral blood lymphocytes (2×10^6 cells/mL) were incubated for 6 days in 10 U/mL interleukin-2 in 10% homologous (or autologous) serum. Cells were harvested and washed three times in cold medium prior to standard ^{51}Cr release assays.

CM — complete medium, LAK — lymphokine-activated killer cells, AS — autologous serum–induced.

*Percentage cytotoxicity at 25:1 effector-target ratio.

†Patient 1 serum.

§Differences between percentage of inhibition of lytic activity of activated peripheral blood lymphocytes induced in untreated serum and that in heat-treated serum.

tion; however, in no instance was inhibitory potential completely reversed to a CM equivalent.

Expression of IL-2R Subunits on Peripheral Blood Lymphocytes. Expression of p55 and p75 was examined simultaneously on pretherapy and posttherapy lymphocytes by single-color and two-color flow cytometry. Analysis of fresh and frozen control lymphocytes showed that both the p75 and p55 receptors were stable in freezing (data not shown). However, single-color as compared with two-color flow analysis showed that in every instance, labeling of the p55 receptor sterically competed with expression of the p75 receptor (Fig 2).

Sequential analysis of p75 and p55 receptors showed a significant decrease in fluorescence intensity of IL-2Rp75 on day 42 of therapy (patient 1). At this time, the patient's lymphocytes were not stimulatable with 10 U/mL of IL-2 (Table 2). Some recovery of receptor and activation potential did return, however, as therapy continued. No significant alteration of the IL-2Rp55 receptor occurred with therapy.

DISCUSSION

This study provides increasing evidence regarding

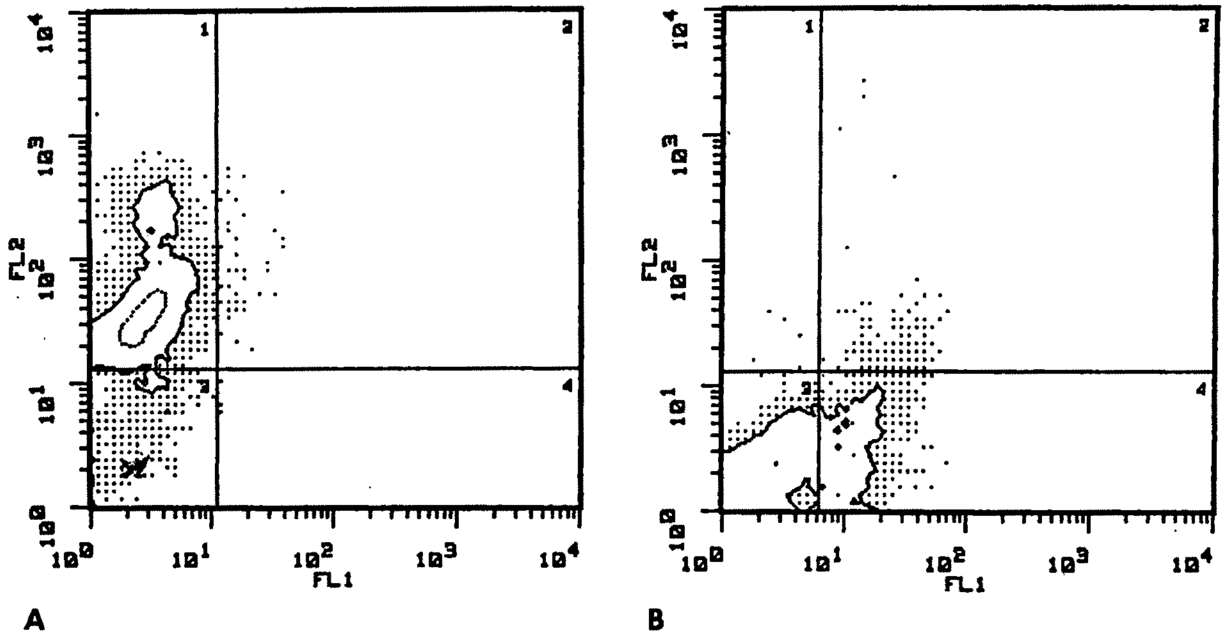

Fig 2. Contour plots. A) Representative single-color IL-2Rp75 plot. B) Corresponding two-color-parameter run plots employing IL-2Rp75 and IL-2Rp55 staining. Two-parameter analysis prevented visualization of previously visualized IL-2Rp75 receptor fluorescence as seen in A.

TABLE 2. INTERLEUKIN-2 RECEPTOR FLUORESCENCE INTENSITY, ABSOLUTE LYMPHOCYTE COUNT, AND STIMULATION POTENTIAL OF PERIPHERAL BLOOD LYMPHOCYTES OBTAINED SEQUENTIALLY FROM TWO PATIENTS DURING INTERLEUKIN-2–INTERFERON-α IMMUNOTHERAPY

Patient No.	*Day of Therapy*	*IL-2Rp75**	*IL-2Rp55**	*LU/10^7 Cells*†	*Absolute Lymphocyte Count*§
1	1	88	27	454	0.9
	8	93	26	356	5.9
	22	91	29	166	14.7
	36	59	5	147	2.1
	42	23	7	<1	9.8
	49	92	23	95	9.0
	56	80	19	57	12.0
	70	70	29	53	2.6
	77	72	30	139	10.2
2	1	40	34	N/A	0.8
	8	35	50	300	0.8
	15	54	40	N/A	1.2
	22	70	40	172	2.4

N/A — not available.

*Expressed as log fluorescence intensity of gated populations.

†Lytic unit (LU) represents number of complete medium 10 U/mL IL-2–induced fresh PBLs required to lyse 25% of target cells.

§Cells x 10^3/mm^3.

the ability of serum from patients with advanced head and neck malignancies both to inhibit the in vitro induction of activated killer cells (expressed as the percentage of activity of medium-treated control cells) and similarly to inhibit the in vitro induction of allogeneic lymphocytes. Although this study showed that some of this serum's inhibitory capacity could be removed by heating at 56°C for 30 minutes, the residual inhibitory capacity supports the theory that multiple substances possess inhibitory potential, as previously reported.[2] Furthermore, the stability of these substances to repeated thawings and freezings was established. Although insufficient serum exists for serum component separation or immunochemical analysis, further studies on similarly treated patients are in order.

Limitations of patient samples often present in studies such as this and create a dilemma in extrapolation of data from a small patient sampling. However, although only two patients could be analyzed in this manner, this report may stimulate further focus or validation of these findings.

The exhibition of induction inhibition independent of lymphocyte source (autologous versus allogeneic) has helped focus attention on serum factors. Although the CM LAK lytic capacity varied depending on lymphocyte source, markedly inhibitory serum reproducibly inhibited lymphocyte activation. The reduction of viability of AS-induced LAK, when greater than 75% inhibitory serum was employed, compared with CM LAK, would support either the development of anti–IL-2 antibodies or IL-2 receptor blockade or the shedding of IL-2 receptor sites. However, as in previous studies, we found no alteration in IL-2Rp55, and although there were changes in IL-2Rp75, CM LAK cells did not reveal decreased viability with lowered p75 receptor fluorescence, as did their counterparts.

Serum induction toxicity to lymphocytes was seen in four other patients who received more than one cycle of therapy.[22] Additionally, inhibition greater than 75% was not seen in patients with squamous cell carcinoma prior to biologic response modifier therapy or in patients used as controls.[23] These inhibitory serum substances that appeared during therapy were also found to be most prominent when systemic IL-2–IFN-α toxicity was greatest.[22] In prior studies, induction inhibition could be temporarily removed by plasmapheresis; we have seen, however, that patients exhibiting markedly inhibitory serum may present in a period of 1 to 3 weeks without inhibitory potential.

Other methods may potentially be employed that may circumvent the evolution of blocking factors. For example, IL-2 analogs have been developed and are presently being analyzed in vitro (E. Grimm, personal communication, 1992). These analogs have directed receptor specificity for the p75 receptor and may reduce the development of blocking factors. By employing different methods, blocking factors may potentially be neutralized, targeted for degradation, or by MAbs prevented from development by means of antisense techniques. All of these methods would require further studies defining these factors and determining their mechanism of inhibition.

Although serum induction inhibition may be reversed in vitro with increasing doses of rIL-2, in vivo institution of escalating doses of rIL-2 is fraught with significant toxicities. Examining this biologic system directed us to investigate the p75 lymphocyte receptor alteration with continuous-infusion rIL-1–IFN-α immunotherapy. In a system that may represent a lymphokine biologic cascade, it appears empiric that a down-regulatory phenomenon might occur in this nonphysiologic lymphokine state. This feedback regulation could produce decreased secretion or production of secondary lymphokines or decreased receptor expression or function. This study did show a discrete trend in p75 fluorescence with therapy. However, with continued rIL-2–IFN-α treatment, variable receptor fluorescence was exhibited. Additionally, some rebound in in vitro induction potential was expressed with increased receptor expression, although not to the lytic potentials expressed earlier in therapy. Importantly, our efforts to perform two-color analysis of the p75 and p55 receptors were unsuccessful. This inability prevented our analysis of the high-affinity receptor. The inhibition of simultaneous receptor expression may be due solely to the bulky nature of immunoglobulin and fluorescent labels with relation to the p75 and p55 receptor sites' proximity.

In summary, this study supports the theory that multiple serum factors are involved in the inhibition of LAK cell induction. Although at least one of these factors was heat-labile, residual serum induction inhibition after heating supports the existence of multiple factors. In addition, although nascent lymphocyte potential varies, the decreased p75 receptor expression seen was related to decreased CM LAK induction capacity at its lowest expression. Some recovery of the p75 receptor fluorescence was seen with continued immunotherapy, although recovery of CM LAK induction capacity recovered incompletely. The relationship of these inhibitory serum factors and p75 receptor expression to the limited clinical response rates of immunotherapy trials remains to be established.

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THIRD INTERNATIONAL SYMPOSIUM ON MENIERE'S DISEASE

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BILATERAL CHOANAL ATRESIA ASSOCIATED WITH MALFORMATION OF THE ANTERIOR SKULL BASE: EMBRYOGENESIS AND CLINICAL IMPLICATIONS

MICHAEL E. DUNHAM, MD ROBERT P. MILLER, MD

CHICAGO, ILLINOIS

A number of craniofacial and systemic malformations have been described in association with choanal atresia. We report a case of bilateral choanal atresia associated with congenital absence of the cribriform plate, crista galli, and perpendicular plate of the ethmoid bone. The anterior skull base defect was detected by using high-resolution computed tomography with three-dimensional reconstructions. The findings support the mesodermal flow theory of choanal atresia, in which there is excess migration of neural crest cells into the developing nasal septum and posterior choanae. This occurs at the expense of cells that would otherwise form the rest of the ethmoid complex. Clinical implications include the need for adequate preoperative imaging of the anterior skull base and consideration of potential intracranial complications during surgical repair.

KEY WORDS — choanal atresia, congenital anomaly, cranial base.

INTRODUCTION

Bilateral choanal atresia is usually part of a generalized malformation of the central maxillofacial structures. Associated anomalies include narrowed nasal cavities due to medial displacement of the lateral nasal walls, arched palate, decreased nasopharyngeal depth, and encephalocele. Choanal atresia has also been reported with craniofacial dysmorphism, including Down, Treacher Collins, Apert, and oral-facial-digital syndromes and Crouzon's disease.

Nasal ethmoidal encephalocele may occur with choanal atresia. However, anterior skull base defects without an encephalocele have not been reported. We present a case of a child with bilateral choanal atresia and a midline anterior skull base defect detected with high-resolution computed tomography (CT). The clinical implications of the defect and its relevancy to existing theories of embryogenesis are discussed.

CASE REPORT

The patient was a boy delivered at term to a 25-year-old G3, P2, A0 mother by repeat cesarean section. His Apgar score was 9/9 at 1 and 5 minutes. In the nursery the child developed tracheal tugging, intercostal retractions, and cyanosis. His respiratory distress responded to intubation with a 3.0-mm (inside diameter) endotracheal tube. The pediatrician was unable to pass a nasogastric tube through either nostril, and the pediatric otolaryngology service was consulted for suspected choanal atresia.

During the initial examination the patient was intubated and breathing spontaneously. His vital signs were normal and his weight was 3.2 kg (50th percentile). A routine eye, ear, nose, and throat examination revealed normal findings. There was no facial dysmorphism. A small feeding catheter could not be passed through either nostril. The chest was clear to auscultation. Heart auscultation revealed a grade 2/6 systol-

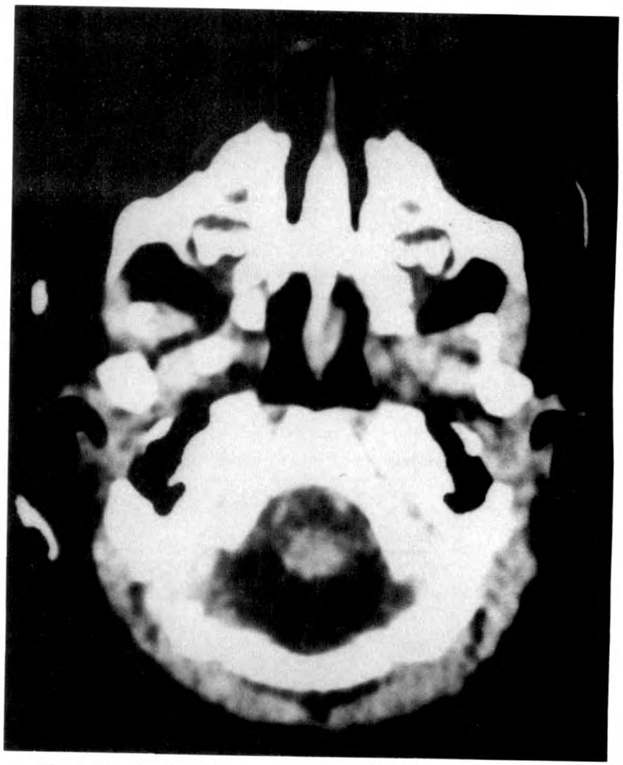

Fig 1. Computed tomogram of nasal cavities demonstrating bilateral bony choanal atresia.

From the Division of Pediatric Otolaryngology, Children's Memorial Hospital, Chicago, Illinois.

REPRINTS — Michael E. Dunham, MD, Division of Pediatric Otolaryngology, Children's Memorial Hospital, Box 25, 2300 Children's Plaza, Chicago, IL 60614.

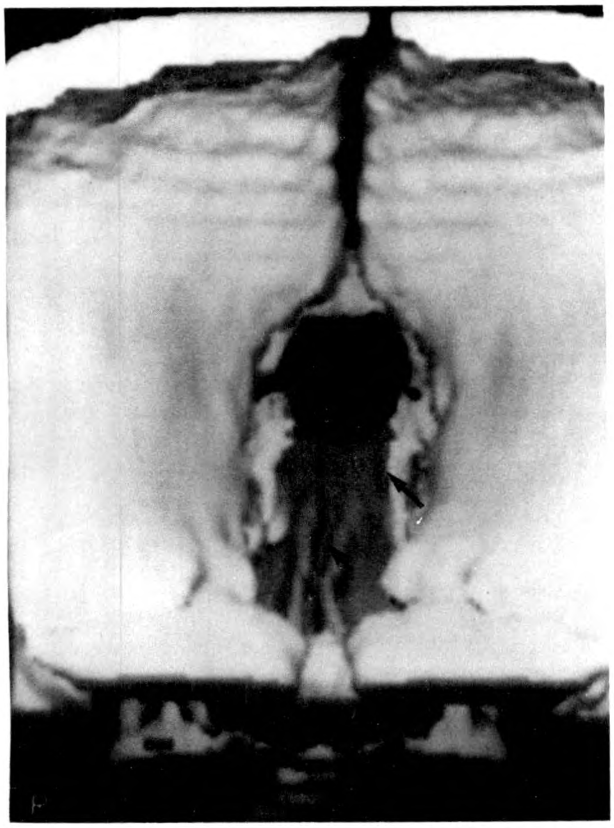

Fig 2. Three-dimensional reconstruction of skull base computed tomogram during contrast cisternography (1.0-mm coronal cuts). Note midline anterior defect with absence of cribriform plate, crista galli, and perpendicular plate of ethmoid bone (long arrow). Note flaring of posterior vomer (short arrow).

ic murmur. The limbs and external genitalia were normal.

Initial laboratory screening tests showed a hemoglobin of 11 g. Hemoglobin electrophoresis was consistent with hemoglobin C trait. The chest radiogram and an echocardiogram were within normal limits. The cardiology service evaluated the patient and felt that there was no evidence of a structural cardiac defect. Results of auditory brain stem evoked testing were normal.

Computed tomography of the nasal cavities was performed with 1.5-mm transverse cuts. Bilateral posterior choanal atresia was confirmed (Fig 1). The atretic plates were bony and were associated with narrowing of the nasal cavities and flaring of the posterior vomer. The radiologist noted a questionable soft tissue density in the nasopharynx on one section.

Contrast (iohexol) cisternography with CT was performed by using 1.0-mm coronal cuts. Subarachnoid contrast did not extend into the nasopharynx, and there was no evidence of a nasal frontal or ethmoidal encephalocele. However, there was absence of the crista galli, cribriform plate, and perpendicular plate of the ethmoid. The midline deformity was demonstrated clearly on the three-dimensional reconstructions of the anterior skull base (Fig 2).

In view of the atretic plate composition and the associated skull base defect, it was felt that immediate transnasal repair was contraindicated. Tracheotomy was performed at age 2 weeks. Direct laryngoscopy and bronchoscopy at the time of the tracheotomy revealed no other airway anomalies. The patient was discharged from the hospital at age 5 weeks.

At age 6 months, the child underwent transpalatal repair of his bilateral choanal atresia (Fig 3). Intraoperative telescopic endoscopy did not reveal a nasopharyngeal mass. The choanae have remained patent

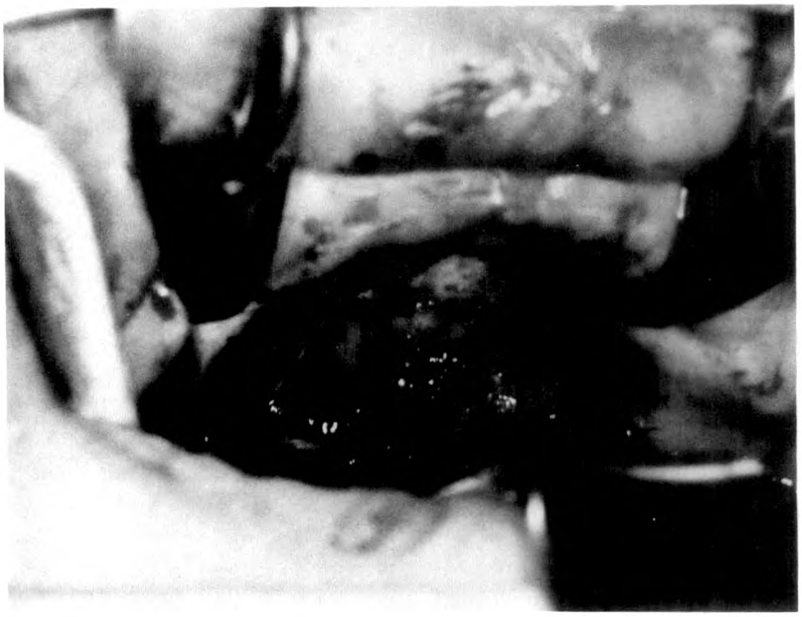

Fig 3. Transpalatal removal of atresia plate.

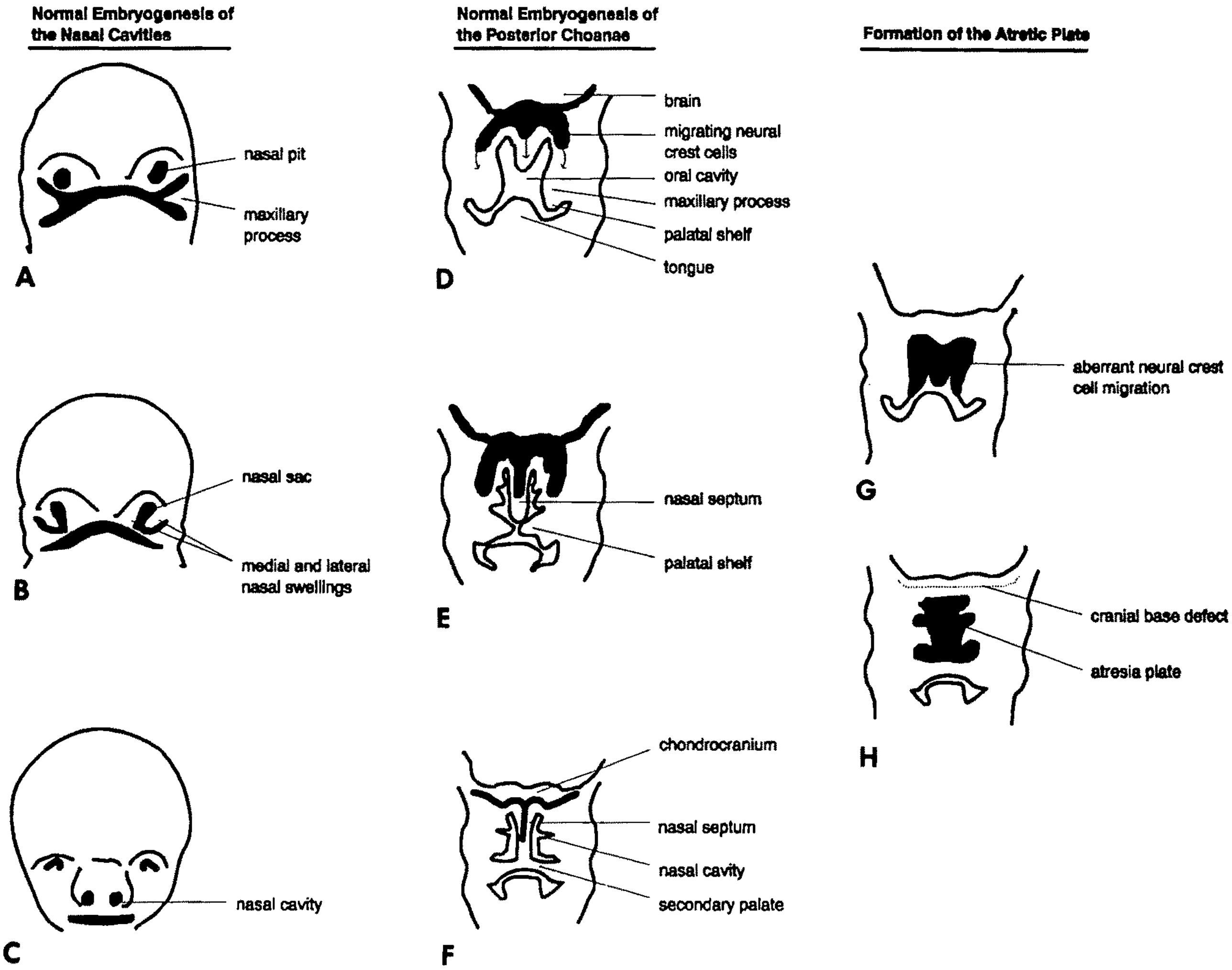

Fig 4. A-F) Normal embryogenesis of A-C) nasal cavities and D-F) posterior choanae. G,H) Aberrant neural crest cell migration and choanal atresia.

through 8 months of follow-up, and the child has been decannulated.

DISCUSSION

Embryogenesis of Choanal Atresia and Skull Base Deformities. During the sixth gestational week, the nasal placodes invaginate to form the nasal pits (Fig 4A). As the surrounding facial mesenchyme grows to form the medial and lateral nasal prominences, the nasal pits deepen and become the nasal sacs (Fig 4B). Initially, the nasal sacs are separated from the oral cavity by the oronasal membrane. The primitive choanae form when the oronasal membrane ruptures and the nasal cavities communicate with the oral cavity at the level of the primary palate. After the palatal shelves fuse to form the secondary palate, the definitive choanae are located at the junction of the posterior nasal cavity and the nasopharynx.

While the membranous nasal cavities are developing, neural crest cells migrate from the dorsal neural folds into the region of the developing facial processes (Fig 4D,E). Once positioned, these cells proliferate rapidly and differentiate into the cartilaginous framework of the skull base and nasal vaults (Fig 4F). The cartilaginous neurocranium, or chondrocranium, forms the early skull base by fusion of several primitive cartilages. These include the paired trabeculae cranii, which form the body of the ethmoid bone and cribriform plate. Later, the bony skull base develops by endochondral ossification of the fused cartilages.

Several theories of abnormal embryogenesis attempt to explain choanal atresia. Most reports mention persistence of the oronasal membrane as the likely cause, but recent authors have recognized defects in this theory. It does not adequately address the craniofacial abnormalities associated with choanal atresia and does not fit existing data regarding the embryogenesis of the CHARGE association.

In 1982 Hengerer and Strome[1] proposed the mesodermal flow theory of choanal atresia. The theory states that there is abnormal migration of neural crest cells into the region of the developing facial processes (Fig 4G). Subsequently, the nasal sacs fail to achieve the proper relationship to the developing nasal vault and never communicate with the nasopharynx (Fig 4H). The mesodermal flow theory adequately explains a number of local anatomic findings associated with choanal atresia, including arched palate, medial displacement of the lateral nasal walls, and decreased nasopharyngeal depth. Abnormal embryogenesis of neuroectodermal cell lines may also explain the anomalies grouped in the CHARGE association.[2]

Considering the mesodermal flow theory, various skull base defects might be expected in children with choanal atresia. Excess migration of nasal crest cells into the developing nasal septum and posterior choanal region might occur at the expense of cells that would otherwise form the rest of the ethmoid complex. Previous reports have documented choanal atresia associated with encephalocele and facial dysmorphism.[3] However, there have been no previous reports of the isolated anterior skull base defect seen in this case. Since detailed imaging of the anterior skull base is usually not part of an evaluation for choanal atresia, previous cases of this defect may have been undetected.

Clinical Implications for Choanal Atresia. Bilateral choanal atresia presents at birth with cyclic respiratory distress aggravated by feeding. If conservative management with an oral airway fails to relieve respiratory obstruction, the infant is intubated and evaluated for other congenital anomalies. The managing surgeon may elect to delay repair until the child is older, if the airway can be maintained through the period of obligate nasal breathing. Cases complicated by multiple anomalies may require tracheotomy.

Computed tomography has become the accepted method for evaluating choanal atresia.[4] Standard transverse CT assesses the position, composition (bony or membranous), and thickness of the atretic plate. It also detects septal malformation and the dimensions of the posterior nasal cavity and nasopharynx. Three-dimensional CT reconstructions have recently improved the surgeon's preoperative assessment of complex craniofacial anomalies. As in the case presented here, they can provide a detailed view of skull base anomalies associated with choanal atresia. Future application of three-dimensional CT may reveal a higher incidence of these deformities than has been previously recognized.

Most of the literature regarding choanal atresia addresses the relative advantages and disadvantages of transnasal or transpalatal repair. The commonly cited advantages of the transpalatal approach are improved exposure and the preservation of mucosal flaps along the newly formed apertures. Transnasal repair requires less operating and convalescent time and does not interfere with the suture lines of the developing palate. Intracranial injury can occur with either approach. However, for patients with anterior skull base deficiencies, the increased exposure available during the transpalatal procedure probably decreases the risk of transcranial injury. In the case presented here, we elected to secure the airway with a tracheotomy because of the severe respiratory distress and the associated skull base deformity. After careful radiographic and endoscopic assessment, the transpalatal repair was accomplished without complications.

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LARYNGEAL ADENOCARCINOMA, NOT OTHERWISE SPECIFIED, TREATED WITH CARBON DIOXIDE LASER EXCISION AND POSTOPERATIVE RADIOTHERAPY

PHILLIP J. HABERMAN, MD
OMAHA, NEBRASKA

REX S. HABERMAN II, MD
MINNEAPOLIS, MINNESOTA

Glandular carcinomas of the larynx are aggressive neoplasms that comprise less than 1% of all laryngeal malignancies. Adenocarcinoma, not otherwise specified, is the most common histologic type. The rarity of these lesions has prohibited clarification of definitive therapy. Traditionally, radical surgery is performed because of the usually high stage at presentation and the relative insensitivity to radiotherapy. A case of glottic T1 adenocarcinoma, not otherwise specified, is reported. The tumor presented clinically as a vocal fold granuloma. The treatment modalities included endoscopic excision with the carbon dioxide laser and postoperative radiotherapy. The patient has been followed up for 39 months without evidence of recurrence or metastases. The current literature is reviewed in regard to treatment of laryngeal glandular carcinomas.

KEY WORDS — adenocarcinoma, carbon dioxide laser, glottis, larynx, review.

INTRODUCTION

Carcinomas of the submucosal seromucous glands of the larynx are very rare lesions that comprise less than 1% of all laryngeal malignancies.[1] In general, these tumors will be referred to as glandular carcinomas instead of the usual term adenocarcinoma. We hope this will avoid any confusion concerning the histologic subtype of adenocarcinoma, not otherwise specified (NOS). Three histologic patterns are most commonly reported: adenocarcinoma NOS (46%), adenoid cystic carcinoma (ACC; 30%), and mucoepidermoid carcinoma (16%).[2] The location of these tumors within the larynx follows the distribution of the laryngeal glands. These glands are particularly concentrated in the false vocal folds and inferior to the anterior commissure.[3] They are only rarely found in the true vocal folds. Correspondingly, most glandular carcinomas are either supraglottic (50%) or subglottic (25%). Only a distinct minority will be glottic.[2] Adenocarcinoma NOS has a distinct predilection for being supraglottic, a fact that sometimes makes partial laryngectomy a possibility with these tumors.[4] Only two cases of glottic adenocarcinoma NOS have been previously reported.[5] The clinical symptoms produced by glandular carcinoma are similar to those of laryngeal malignancies in general. Most lesions are large, nonulcerated masses causing sore throat, hoarseness, dysphagia, and/or airway obstruction. They are aggressive neoplasms, usually stage III or IV at presentation, with frequent cervical lymph node and distant metastases.[5-7] The most common distant metastatic sites include liver and lung. Average survival is approximately 2 years,[5] and the 5-year survival rate is a dismal 17%.[6] Because laryngeal glandular carcinomas are so rare, only anecdotal reports describing treatment have been reported. The most widely recommended therapy has been radical surgery.[4,5,7,8]

In carefully selected patients, endoscopic laser excision is a proven form of therapy for glottic T1 squamous cell carcinoma of the larynx.[9] No experience with this technique has been previously reported for any early glandular carcinoma of the larynx. We report a case of glottic T1 adenocarcinoma NOS treated with endoscopic laser excision and postoperative radiotherapy. No recurrence or metastasis has occurred in 39 months of follow-up.

CASE REPORT

A 74-year-old man presented with a 3-month history of persistent hoarseness. No history of dysphagia, odynophagia, or otalgia was obtained. He had smoked one pack of cigarettes per day for 40 years, but had quit smoking 2 years prior to presentation. There was no history of alcohol abuse. He had previously undergone surgery that included endotracheal intubation. This intubation was not prolonged. There was no history of malignant disease. Examination by fiberoptic nasopharyngeal laryngoscopy demonstrated what appeared to be a vocal fold granuloma. The lesion was polypoid, nonulcerated, and 1.0 cm in greatest dimension and arose from the posterior third

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From the Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska (P. J. Haberman), and the Department of Otolaryngology–Head and Neck Surgery, University of Minnesota Medical Center, Minneapolis, Minnesota (R. S. Haberman II).

REPRINTS — Phillip J. Haberman, MD, Dept of Pathology and Microbiology, University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198.

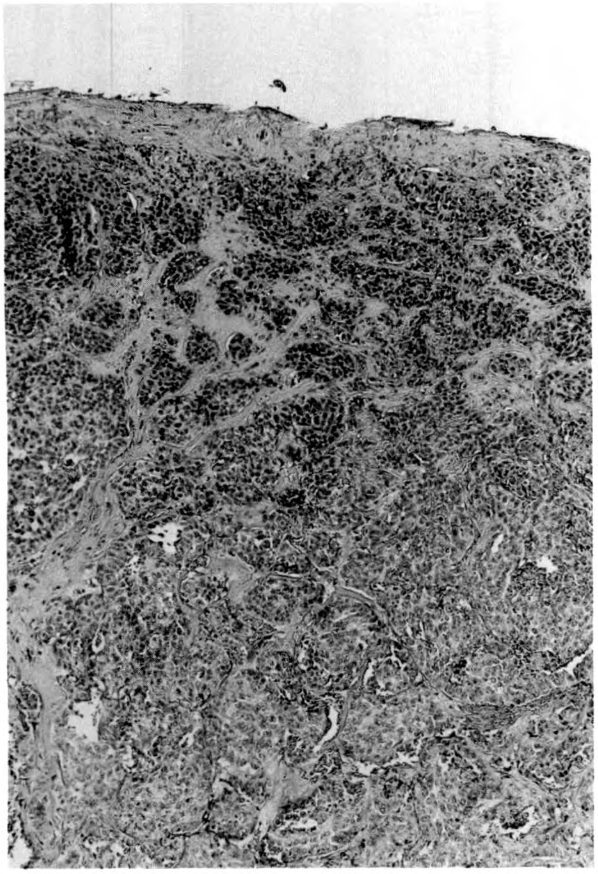

Fig 1. Poorly differentiated adenocarcinoma infiltrating glottic submucosa with atrophy of overlying squamous epithelium (H & E, original x40).

of the left true vocal fold. Normal vocal fold tissue completely surrounded the mass. Both true vocal folds were completely mobile. The remainder of the physical examination was negative. The patient was taken to the operating room, where direct microlaryngoscopy was performed with excision of the mass using carbon dioxide (CO_2) laser. By using 6 to 8 W of power and a 0.1-second pulse duration combined with an interrupted mode, the lesion was excised to the depth of the vocalis muscle. Because it was felt clinically that the lesion was benign, no frozen section evaluation of the surgical margin was performed.

Permanent histologic sections revealed an infiltrative, poorly differentiated adenocarcinoma with atrophy of the overlying squamous epithelium (Fig 1). The tumor is distributed in the glottic submucosa in variable-size nests and cords delimited by a desmoplastic stroma. The malignant cells are haphazardly arranged, with focal abortive gland formation (Fig 2). The nuclei are of various sizes and are round to oval, with vesicular chromatin and a single, conspicuous, round nucleolus (Fig 3). The cytoplasm is amphophilic, present in scant to moderate amounts, and vacuolated. Scattered tumor cells and glands contain mucicarmine-positive material. Immunoperoxidase staining for prostatic acid phosphatase, prostate-specific antigen, and B72.3 was negative.

The patient received 66 Gy of irradiation postoperatively. He is currently 39 months posttherapy with no evidence of recurrence or metastasis. Additionally, he has excellent laryngeal function.

DISCUSSION

Glandular carcinomas of the larynx are uncommon malignancies. Toomey's[6] review dating from 1870 to 1967 contained 96 cases. Approximately 110 cases have been reported since 1967.[2,4,5,7,8,10,11] The experiences by various authors with these lesions have been so sporadic that no series has been large enough for statistical evaluation of therapy. Thus, only generalities concerning treatment have been forthcoming.

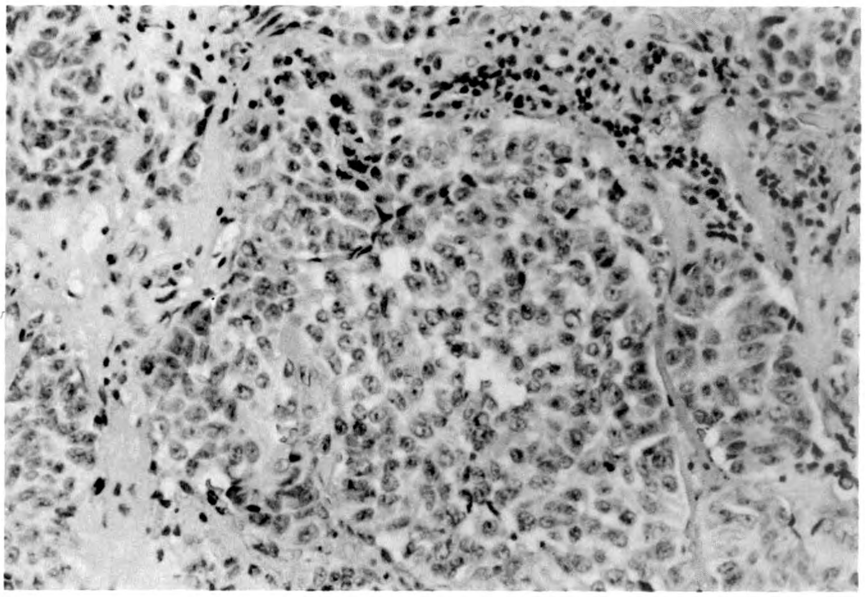

Fig 2. Variable-size nests of haphazardly arranged tumor cells with focal abortive gland formation (H & E, original x200).

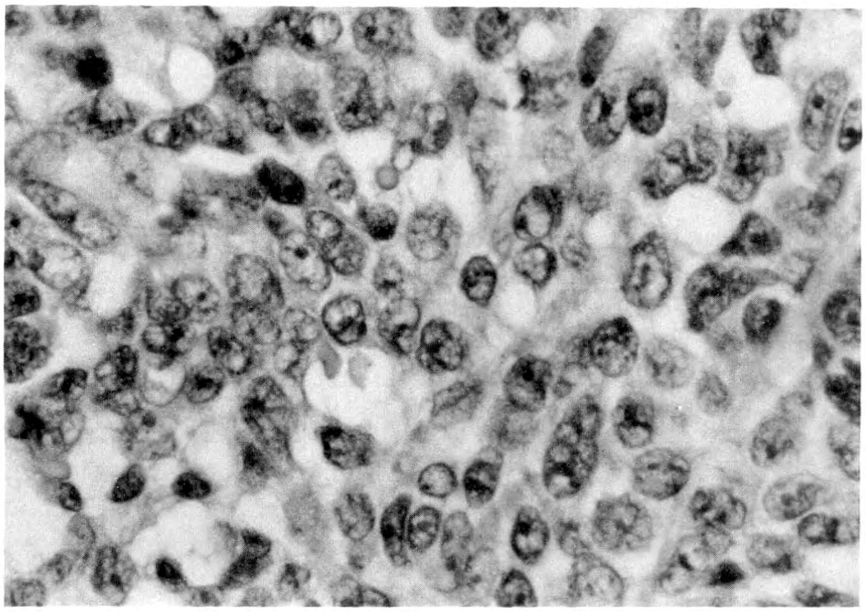

Fig 3. Malignant nuclear features, cytoplasmic vacuolization, and abortive gland formation (H & E, original x400).

Radical surgery is the favored form of therapy, probably because of the propensity for these lesions to present at an advanced clinical stage. Surgery was the primary form of treatment in 70% of the 37 detailed cases in Toomey's[6] report. Half of these patients received total or subtotal laryngectomy, with or without radical neck dissection. Incomplete figures and inadequate follow-up data precluded determination of the response to surgery or other forms of treatment. Available data indicate the 5-year survival was 17%. Radical surgery was observed to give the best chance for cure.

Cady et al[7] reported 31 cases of nonepidermoid laryngeal cancer, 17 of which were glandular carcinomas. Aggressive therapy was recommended, consisting of total laryngectomy with radical neck dissection on the side of the primary lesion for all stages of disease. The reason for inclusion of a radical neck dissection was that 13 of 17 (76%) of their patients with glandular carcinoma developed cervical lymph node metastases. Eight of these patients had clinically positive lymph nodes on presentation. Of the 9 patients with initially negative nodes, 5 later developed cervical metastases.

Twenty-seven cases of glandular carcinoma of the larynx were reported by Whicker et al.[4] Their experience suggested that the extent of surgical resection may be based on the histologic type of tumor encountered. Their patients could be divided into two groups: 1) those with ACC (9 patients), and 2) those with another type of glandular carcinoma (12 of 18 patients had adenocarcinoma NOS). Those patients with ACC differed in their clinical presentation. Most significantly, 8 of 9 cases were subglottic, as opposed to 11 of 12 cases of adenocarcinoma NOS that were supraglottic. Also, patients with ACC had enlarged cervical lymph nodes much less frequently (10% versus 66%), and they had double the average survival (8.5 years versus 4.3 years). However, death from recurrent or metastatic ACC was typically inevitable. Tumor recurrences up to 15 to 20 years following initial therapy were seen. These factors led to the conclusion that conservative therapy should rarely be performed on patients with ACC of the larynx. Because of the supraglottic predilection of adenocarcinoma NOS, supraglottic laryngectomy was suggested as a possibility, given the proper stage of disease for conservation surgery. Although 20 of the 24 patients in their series in which survival data were valid died of their disease, radical surgery was suggested as the type of treatment that would give the best chance for cure.

In their report of eight cases of glandular carcinoma of the larynx, Sessions et al[10] related that the length of survival was not dependent on histopathology, stage, or mode of therapy. The most conservative therapy possible was thus recommended for primary treatment.

Spiro et al[5] had 20 patients with glandular carcinoma of the larynx, 18 of whom were treated. Surgery was the primary form of therapy. Laryngectomy was performed in 13 cases, and 9 patients received radical neck dissection. One patient had an epiglottectomy, and another received local excision of a recurrence via laryngofissure. One of the treated patients died postoperatively and thus must be excluded from survival figures. Of the 17 remaining patients, 11 (65%) died as a direct result of local or metastatic disease. Four died of other causes less than 1 year after initial treatment. The 2 patients who were apparently "cured" were alive 10 and 11 years after treatment. One received laryngectomy, and the other laryngectomy and radical neck dissection. Both had stage I lesions, the only such tumors in this series. From this experience, the suggestion was made that perhaps more aggressive treatment with either radical neck dissection and/or irradiation would have improved results.

The experience with radiotherapy for laryngeal glandular carcinomas has been much less extensive and less effective than the surgical approach. Five of the 29 patients included in Toomey's[6] literature review received radiotherapy alone. As mentioned, the incompleteness of the data on these individuals precludes a meaningful statement on the effectiveness of this form of therapy. However, 1 patient in this series seemed to have been "cured" of disease with irradiation alone. The lesion was a stage I, supraglottic, poorly differentiated adenocarcinoma. The patient was alive and well 10 years after therapy. Whicker et al[4] had the largest collection of patients treated by irradiation. Nine of 27 patients received irradiation only. None had favorable results. One of 5 patients reported by Eschwege et al[8] received only radiotherapy because of pulmonary metastases at presentation. She survived at least 5 years after treatment with slowly progressing lung lesions. Two of the 18 patients treated by Spiro et al[5] received irradiation as initial therapy. One patient died 6 months later secondary to hemorrhage due to radionecrosis, while the other survived nearly 6½ years, finally succumbing to local disease. Thus, it seems irradiation may be effective in early laryngeal glandular carcinoma, and perhaps as a form of palliative therapy.

Experiences with chemotherapy for glandular carcinomas of the larynx have been so few as to inhibit meaningful comment. Spiro et al[5] used chemotherapy for one patient with already disseminated disease. She survived for 3 months.

Our case is unusual because of its location and early stage. Six other glottic glandular carcinomas were mentioned in a review by Bloom et al.[2] Only two of these were adenocarcinoma NOS. Stage I lesions reported in the literature were uniformly associated with a good outcome. Examples include the stage I lesion commented on in Toomey's[6] series. The patient with an apparent T1 pyriform sinus adenocarcinoma NOS reported by Cady et al,[7] and treated with laryngectomy and radical neck dissection, was free of disease after 6 years of follow-up. Dogra[11] reported a supraglottic stage I lesion treated with laryngofissure. The patient was alive and well 9 years later without recurrence. The only "cures" in Spiro et al[5] were of stage I tumors. The case of moderately well-differentiated adenocarcinoma NOS limited to the midportion of the laryngeal epiglottis reported by Bloom et al[2] was treated with epiglottectomy. The patient was disease-free at 2½ years of follow-up. This seems to suggest that early laryngeal glandular carcinomas are associated with a good prognosis. Perhaps minimal surgery and/or irradiation could be quite adequate therapy for these lesions. Our experience supports this hypothesis.

Intralaryngeal surgery via suspension laryngoscopy for vocal fold malignancies was presented as deserving "serious consideration" by LeJeune[12] in 1946. As long as strict criteria were met, this approach to early vocal fold tumors produced good results. The criteria were that the growth be 1) in the early stages of development, 2) small in size, 3) limited to one vocal fold, and 4) completely surrounded by normal vocal fold tissue. Of the 39 patients in the series by LeJeune who met these criteria, 36 were without disease, with most having up to 5 years of follow-up. LeJeune stated that 95% of the tumors were of the squamous cell variety. No other reference to histology was made.

The use of the CO_2 surgical laser and microscope for transoral excision of T1 glottic "carcinomas" was shown by Strong[13] in 1975 to be an optimal treatment method for these lesions. He reported excellent initial results on 11 cases. Long-term results were not yet available. Three-year follow-up data on 35 cases of T1 glottic squamous cell carcinoma treated by excisional biopsy using the CO_2 laser were provided by Blakeslee et al[9] in 1984. Prerequisites for this type of therapy included 1) that the patients be medically eligible for endoscopic surgery using suspension laryngoscopy, 2) that adequate exposure be obtained so the entire lesion could be visualized, and 3) that the lesion be confined to the true vocal fold. The excisional biopsy was not deemed complete until no residual tumor was present under the operating microscope and surgical margins were free, both in frozen and permanent histologic sections. By these criteria, 31 of 35 (89%) patients survived 3 or more years without disease. The series also included 12 patients with verrucous carcinomas and 3 with spindle cell carcinomas, all of whom were without recurrence at 3 years. The overall 3-year survival rate without recurrence was thus 92% (46 of 50). Also, as with our patient, the laser seemed to leave these patients with good voice quality postoperatively.

As can be clearly seen from the data reviewed, transoral excisional biopsy using the CO_2 laser is an excellent therapeutic approach for T1 glottic squamous cell carcinoma, verrucous carcinoma, and perhaps spindle cell carcinoma. However, until now no experience with this technique has been reported for early glandular carcinomas of the larynx. Although the margins of resection in our case were not examined by frozen section, it is hoped that if residual tumor was left in the patient following surgery, the postoperative radiotherapy has effected a cure. Considering the reported experiences with early glandular carcinoma, and the effectiveness of transoral CO2 laser excisional biopsy on other tumor types, 39 months of follow-up without recurrence seems to indicate that this patient's prognosis should be good.

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AMERICAN DIOPTER AND DECIBEL SOCIETY

The American Diopter and Decibel Society will hold its biennial meeting January 16-23, 1993, at the Westin Camino Real in Puerto Vallarta, Mexico. Abstracts are currently being accepted. For further information, contact Robin L. Wagner, American Diopter and Decibel Society, 3518 Fifth Avenue, Pittsburgh, PA 15213; fax (412) 647-8720, phone (412) 647-2227.

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1993 CONFERENCE ON IMPLANTABLE AUDITORY PROSTHESES

The 1993 Conference on Implantable Auditory Prostheses will be held July 11-15, 1993, on the campus of Bryant College in Smithfield, Rhode Island. This is the sixth in a series of biennial research conferences originating with the 1983 Gordon Conference. The meeting will provide a forum for close interaction among scientists in all disciplines relating to the field of cochlear implants. For further information, contact Chris van den Honert, Division of Otolaryngology–Head & Neck Surgery, Box 3550, Duke University Medical Center, Durham, NC 27710; Telephone: (919) 684-6099, E-Mail: chx@dukehrl.mc.duke.edu.

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FACIAL CANAL DEHISCENCE: HISTOLOGIC STUDY AND COMPUTER RECONSTRUCTION

HARUO TAKAHASHI, MD
KYOTO, JAPAN

ISAMU SANDO, MD, DMSC
PITTSBURGH, PENNSYLVANIA

The incidence, location, shape, and dimensions of dehiscences in the facial canal to the middle ear space were studied in 160 temporal bones obtained from 129 individuals 24 gestational weeks to 109 years of age at death by means of light microscopy and our computer reconstruction and measurement method. Dehiscences were observed in 95 of the 129 individuals (74%) and in 119 of the 160 bones (74%). The incidence was found to be quite high among fetuses and newborns, lowest in individuals in their twenties and then again quite high in the geriatric population (χ^2 test, $\chi^2 = 5.45$ and 4.41, $p < .05$). The most frequent site of dehiscence was the oval window area, particularly in its posterior half (57% of all ears) on the inferior to inferomedial aspects of the canal; these dehiscences were clearly demonstrated in reconstructed images. The incidence of dehiscence in the area of the cochleariform process was 16%, and all these dehiscences were on the lateral to superolateral aspect of the canal. The second genu area and the mastoid portion were sites of dehiscence in 21% and 18%, respectively, of specimens; more than half of the dehiscences in the second genu area and mastoid portion were on the lateral to anterolateral and posterior aspects of the facial canal, respectively. The shape of the dehiscence tended to be oval in the oval window area, but rather irregular in the other areas. The dehiscences ranged from 0.4 to 2.64 mm in length, from 0.12 to 1.59 mm in width, and from 0.03 to 1.87 mm^2 in surface area. The proximity of these dehiscences to the field of otologic surgery is stressed.

KEY WORDS — computer three-dimensional reconstruction, facial canal dehiscence, temporal bone histopathology.

INTRODUCTION

The facial nerve is one of the most significant and vulnerable structures in the temporal bone. This nerve is at risk during surgical procedures involving the inner ear and/or middle ear, and especially so when there is dehiscence of the facial canal on its middle ear side, because such dehiscence increases the possibility of unexpected postoperative facial nerve complications. Having precise information about the facial canal dehiscences is considered of prime importance to otologic surgeons in avoiding such complications, but although there have been several reports on this subject,[1-9] to our knowledge none has provided detailed topographic data or three-dimensional (3-D) views and dimensions of such dehiscences — information that would be of very great help to otologic surgeons in picturing the anatomy of the area as they may encounter it at operation.

In the study reported here, an attempt was made to clarify the age-related incidence, and to detail the location, shape, and dimensions of facial canal dehiscences by both light microscopy and the computer-aided 3-D reconstruction and measurement method we developed.[10,11]

MATERIALS AND METHODS

The materials (serial histology sections) we used in this study were from 160 temporal bones obtained from 129 individuals 24 gestational weeks to 109 years old at death. None of the individuals had a history of congenital anomaly or osteolytic diseases such as systemic bone disease, malignant external otitis, or cholesteatoma. All specimens were processed for histologic study according to the technique described by Sando et al[12] to provide serial 20- to 30-μm-thick horizontal (105 bones) or vertical (55 bones) sections.

For this study, facial canal dehiscence was defined as an opening in the bone between the facial canal and any middle ear space, without interposition of a major anatomic structure such as the tensor tympani muscle or the stapedius muscle, and with only a thin layer of connective tissue and the middle ear mucosa between the facial nerve and the middle ear space. The bony opening in the facial canal from which the branch of the superficial petrosal artery exits to the stapes was not included in this definition.

Light Microscopy. Every 10th histologic section was studied by light microscopy. The overall incidence of dehiscence and age-related incidence were determined, and the location of each dehiscence was described, not only in the longitudinal but also in the cross-sectional plane (ie, posterior part of the oval window area and on the inferior aspect of the canal).

From the Elizabeth McCullough Knowles Otopathology Laboratory, Division of Otopathology, Department of Otolaryngology, University of Pittsburgh School of Medicine, Eye and Ear Institute of Pittsburgh, Pittsburgh, Pennsylvania. Dr Takahashi is currently at the Department of Otolaryngology, Kyoto University Faculty of Medicine, Kyoto, Japan. This study was supported by research grant 5 RO1 DC00123 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

REPRINTS — Isamu Sando, MD, DMSc, Division of Otopathology, Eye and Ear Institute of Pittsburgh, 203 Lothrop St, Pittsburgh, PA 15213.

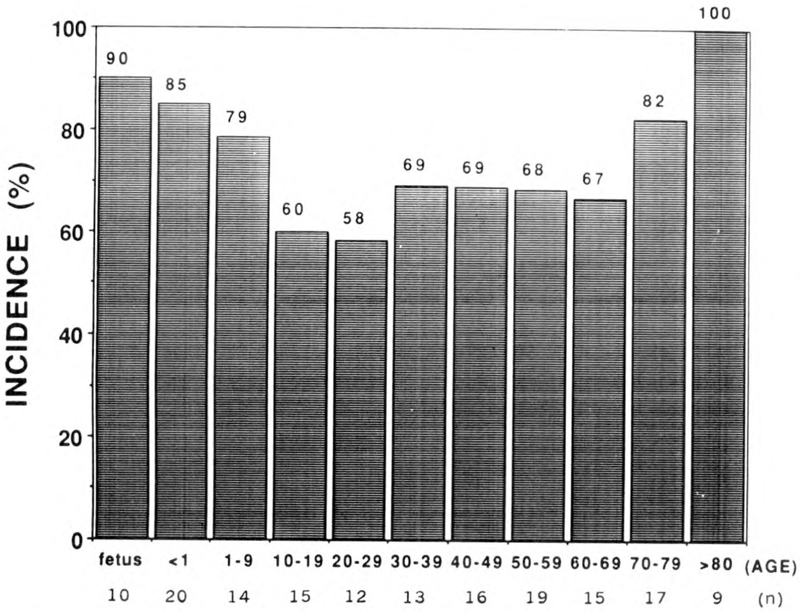

Fig 1. Incidence of facial canal dehiscence as function of age. n — number of ears in each age group.

Three-dimensional Reconstruction. For the computer-aided 3-D reconstruction and measurement portion of the study, 20 temporal bones obtained from 19 individuals between 1 day and 72 years of age were evaluated. The equipment we used consisted of a personal computer (NEC 98-RL, model 5), a high-resolution color monitor (1,120 x 750 pixels), a digitizer (Hitachi HDG-1515) with resolution set at 0.1 mm, and a printer. The software we used was developed by Takagi and Sando.[10,11] The outlines of the facial canal, the facial canal dehiscence, and the footplate of the stapes were reconstructed for each specimen by using the 3rd through the 10th histology sections. The 3-D location (particularly in relation to the stapes footplate) and shape of each dehiscence were noted; in addition, its length (along the axis of the facial canal), width (in the cross section of the canal), and surface area were measured. Details of the procedures for 3-D reconstruction and measurement were described previously.[10,11,13,14]

RESULTS

Light Microscopy. Dehiscences of the facial canal were observed in 95 of the 129 cases (74%) and in 119 of the 160 temporal bones (74%). Figure 1 shows how the age-related incidence of the dehiscences, which was found to be quite high among fetuses (90%) and newborns (85%), showed a gradual decrease to a nadir in individuals in their twenties (58%) and then increased again in middle-aged and geriatric populations (67% to 100%). The differences were statistically significant in incidences of dehiscence 1) in fetuses and children younger than 9 years versus in adolescents and young adults (between 10 and 29 years of age; χ^2 test, $\chi^2 = 5.45$, $p < .05$) and 2) in adolescents and young adults versus the geriatric population (over 70 years of age; χ^2 test, $\chi^2 = 4.41$, $p < .05$).

A total of 186 facial canal dehiscences were identified in 119 (74%) of the total 160 ears examined. Table 1 shows the distribution of dehiscences along the facial canal and with regard to the dominant aspect in cross section of the facial canal. In the cochleariform process area, dehiscences were observed in 26 ears (16% of the total ears), and all of these dehiscences were on the lateral or superolateral

TABLE 1. SITES OF 186 FACIAL CANAL DEHISCENCES IN 119 OF 160 EARS

Area Involved	*No. of Dehiscences*	*Percentage of All (160) Ears*	*Aspect**
Cochleariform process area	26	16%	Lateral to superolateral (26/26, 100%)
Oval window area	97	61%	
Anterior only	7	4%	Lateral (13/18, 72%)
Posterior only	79	49%	Inferior to inferomedial (75/90, 83%)
Both	11	7%	
Second genu area	34	21%	Lateral to anterolateral (19/34, 56%)
Mastoid portion	29	18%	Posterior (16/29, 55%)

*Dominant aspect of dehiscence in cross section of facial canal.

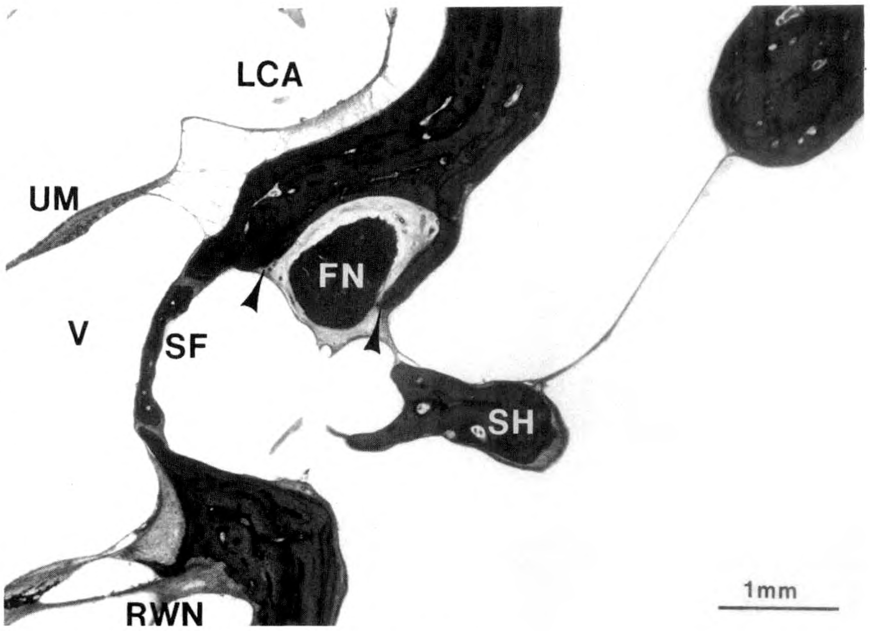

Fig 2. Photomicrograph (anterior-posterior view) of left facial canal and surrounding structures (vertical section) of 4-year-old boy showing dehiscence (between arrowheads) on inferior aspect of oval window area. FN — facial nerve, LCA — lateral semicircular canal ampulla, SF — stapes footplate, SH — stapes head, RWN — round window niche, UM—utricular macula, V—vestibule.

aspect of the facial canal. In 97 ears (61% of the total ears) a dehiscence was present in the oval window area, and most of these dehiscences (90 of 160 or 56%) were in the posterior half of this area (posterior to the center of the stapes footplate). In 83% of the ears in which the dehiscence was in the posterior half of the oval window area (42% of the total ears), the dehiscence was on the inferior to inferomedial aspect of the facial canal in cross section (Fig 2). In contrast, a dehiscence was found in only 18 ears (11% of the total ears) in the anterior half of the oval window area; further, in 72% (13 ears) in which the dehiscence was in this area it was on the lateral aspect of the facial canal. A dehiscence was present in the second genu area or in the mastoid portion in 34 ears (21% of the total ears) and in 29 ears (18% of the total ears), respectively. Approximately half (56%) of the dehiscences in the second genu area were on the lateral to anterolateral aspect of the facial canal, opening directly into the facial recess (Fig 3); 24% of them were on the anterior aspect of the canal, opening into the tympanic cavity; and the remaining 20% were on the medial or posterior aspect of the canal, opening into the mastoid air cells. Of dehiscences in the mastoid portion of the facial canal, about half (55%) were on the posterior aspect of the canal and opened into the mastoid air cells; 34% were on the lateral aspect and opened into the facial recess; and the remaining 11% were on the medial or anterior aspect of the facial canal and opened into the tympanic sinus or tympanic cavity, respectively.

Three-dimensional Reconstruction. Facial canal dehiscences were found in a total of 34 sites in the 20 temporal bones reconstructed; 5 (15%) were found in the cochleariform process area, 24 (70%) in the oval window area, 3 (9%) in the second genu area, and 2 (6%) in the mastoid portion (Table 2). Figure 4 shows the length and location of the 24 facial canal dehiscences in the oval window area relative to the stapes footplate. As Fig 4 shows, most of the dehiscences (21 of 24 or 88%) were located posterior to the center of the stapes footplate. The dehiscences tended to be oval in shape (15 of 24 or 63%) in the oval window area (Figs 5 and 6A), but of various shapes in other areas (Fig 6B). It was also found that most of the dehiscences (21 of 24 or 88%) were on the inferior to inferomedial aspect of the canal (Figs 5B and 6A).

Table 2 also shows the ranges and averages of the dimensions of the 34 facial canal dehiscences reconstructed and measured. Dehiscence length ranged from 0.4 mm to 2.64 mm; the longest dehiscence and the greatest mean value for dehiscence length were in the oval window area. Dehiscence width ranged from 0.12 mm to 1.59 mm; dehiscences in the mastoid portion were widest. Dehiscence areas ranged from 0.03 mm^2 to 1.87 mm^2; the largest dehiscence in this series was in the oval window area, but the average dehiscence size was greatest in the mastoid portion.

DISCUSSION

The gross incidence of facial canal dehiscence as determined in the present study (74%) is the largest ever reported, although reported incidences vary considerably (7% to 58%).[1-7] As might be expected, light microscopic studies reveal a higher incidence of dehiscence (15% to 58%)[2,5-7] than the other methods of observation such as gross dissection (15%)[1] or operative microscopic examinations during surgery (7%).[3] It is notable that we found the incidences of

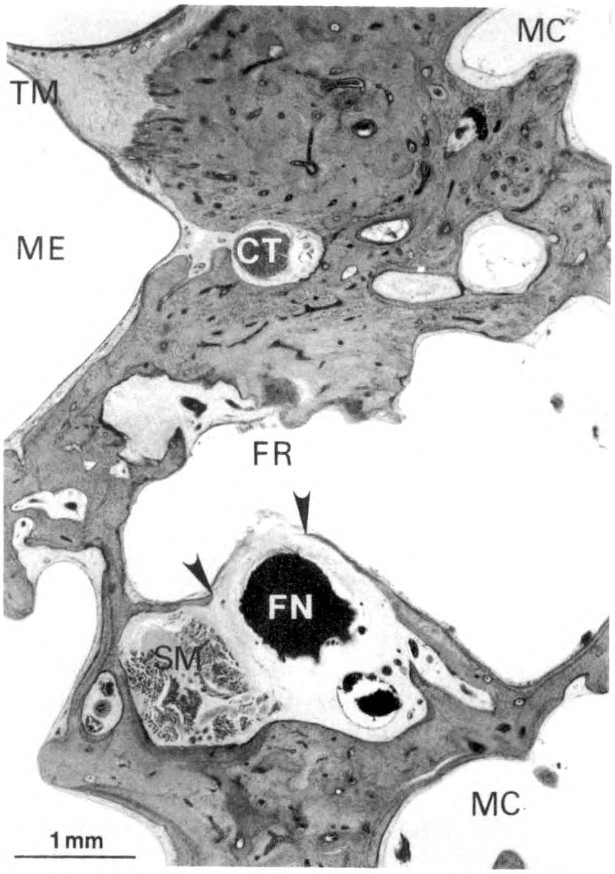

Fig 3. Photomicrograph (superior-inferior view) of right facial canal (horizontal section) of 57-year-old man showing dehiscence (between arrowheads) in second genu area. Note that facial nerve (FN) is widely exposed to facial recess (FR). CT — chorda tympani nerve, MC — mastoid air cells, ME — middle ear cavity, SM — stapedius muscle, TM — tympanic membrane.

dehiscence in the second genu and the mastoid portion to be particularly greater than those revealed by previous similar histologic studies.[7]

What we found of great significance to otologic surgeons is that some 40% of all dehiscences were on the inferior to inferomedial aspect of the canal in the posterior half of the oval window area, where they may readily be encountered during middle and/or inner ear surgery. Particularly during stapes surgery, surgeons should be aware that dehiscences of the facial canal are often located not only just posterosuperior to the stapes, but also on the inferior to inferomedial aspect of the canal — the aspect that faces the surgical field. There have been several reports in the literature that the most frequent location of facial canal dehiscence is adjacent (superior) to the oval window.[2-4,6-9] Nager and Proctor,[9] however, pointed out that dehiscences are particularly likely posterior to the oval window. In the present study, this was clearly shown by the results of computer reconstruction and measurement.

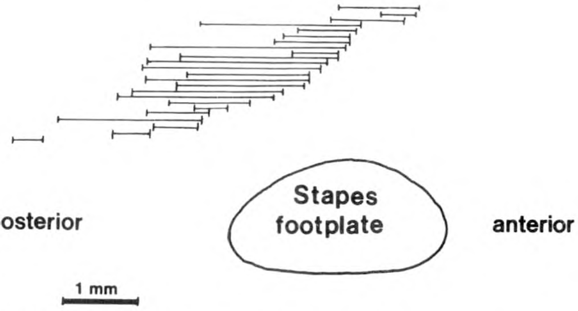

Fig 4. Schematic representation of length and location in relation to stapes footplate of 24 reconstructed facial canal dehiscences in oval window area. Note that most dehiscences are posterior to median of stapes footplate.

Some interesting findings of the present study were that 1) most dehiscences were on the superolateral or lateral aspect of the facial canal when they occurred in the anterior tympanic portion (cochleariform process area and anterior half of the oval window area), but 2) in the posterior part of the tympanic portion, the most frequent site of dehiscence was on the inferior to inferomedial aspect of the canal, and 3) the lateral or posterior aspect was most frequently involved by dehiscence in the peripheral parts of the facial canal (the second genu area and mastoid portion).

We have two comments regarding these results. First, the findings show that surgeons should be watchful for dehiscences, not only during stapes surgery, but also when manipulating the tympanic cavity during tympanoplasty, during cochlear implant surgery through a facial recess approach, and

TABLE 2. DIMENSIONS OF 34 FACIAL CANAL DEHISCENCES

Area Involved	*No. of Dehiscences*	*Length (mm)*	*Width (mm)*	*Area (mm^2)*
Cochleariform process area	5	0.84 ± 0.91 (0.4 to 2.43)	0.53 ± 0.38 (0.23 to 1.14)	0.47 ± 0.46 (0.07 to 1.27)
Oval window area	24	1.41 ± 0.74 (0.42 to 2.64)	0.54 ± 0.26 (0.12 to 1.06)	0.66 ± 0.59 (0.03 to 1.87)
Second genu area	3	0.92 ± 0.34 (0.49 to 1.34)	0.23 ± 0.02 (0.2 to 0.27)	0.15 ± 0.03 (0.12 to 0.21)
Mastoid portion	2	1.12 ± 0.04 (1.08 to 1.17)	1.43 ± 0.16 (1.27 to 1.59)	1.52 ± 0.04 (1.48 to 1.56)

Values are mean ± SD; values in parentheses are ranges.

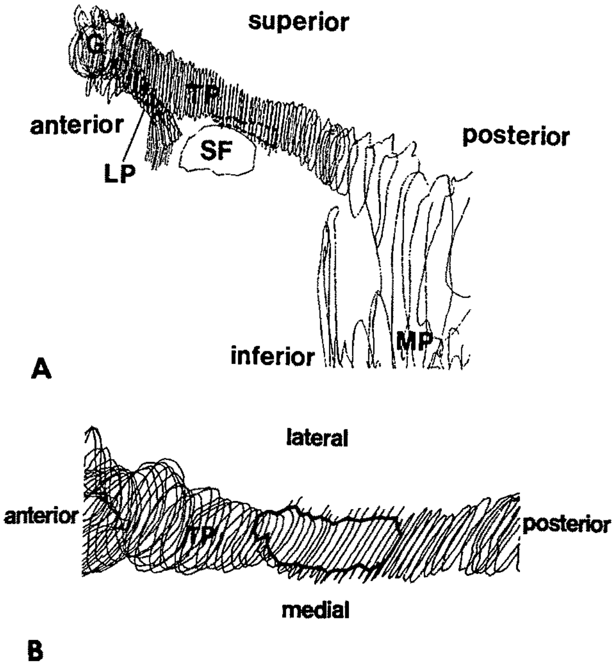

Fig 5. Computer-reconstructed images (left ear of 3-year-old girl). TP — tympanic portion of facial canal. A) Lateral view of facial canal and dehiscence (dashed line) on inferior aspect of facial canal (behind canal in this view) in posterior part of oval window area. G — geniculate area of facial canal, LP — labyrinthine portion of facial canal, MP — mastoid portion of facial canal, SF — stapes footplate. B) Close-up view of dehiscence from inferior direction. Note that dehiscence is oval.

during cortical mastoidectomy, because the dehiscences tend to face every surgical field just mentioned.

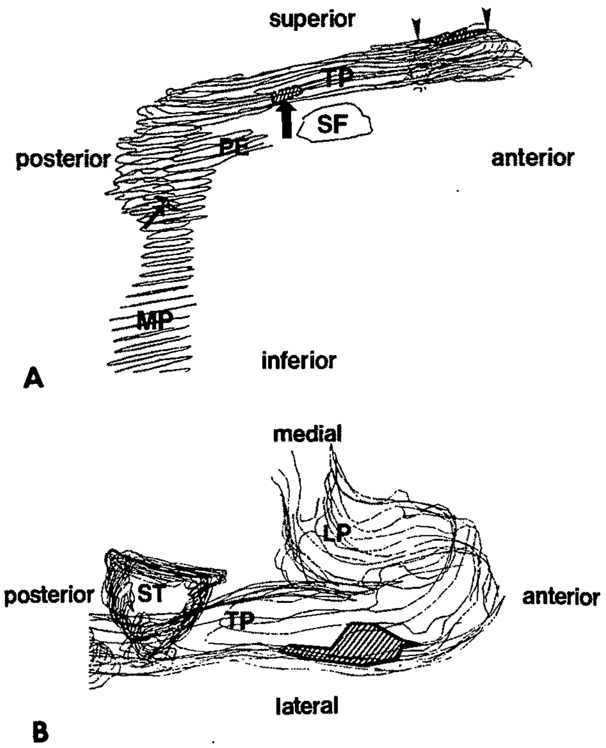

Fig 6. Computer-reconstructed images (right ear of 59-year-old woman). TP — tympanic portion of facial canal. A) Lateral view of facial canal with dehiscences on superolateral aspect of cochleariform process area (between arrowheads), on inferomedial aspect of posterior half of oval window area (large arrow; dashed line indicates that dehiscence is on opposite side of facial canal from that viewed), and on lateral aspect of second genu area (small arrow). PE — pyramidal eminence, MP — mastoid portion of facial canal, SF — stapes footplate. B) Close-up view from superior direction of irregularly shaped dehiscence (hatched area) in cochleariform process area of facial canal. LP — labyrinthine portion of facial canal, ST — stapes.

Second, it is interesting to discuss this variety in cross-sectional location of dehiscences in relation to development of the facial canal. The origin of the facial canal has been reported to be a sulcus on the lateral surface of the primordial otic capsule.[9,15] With regard to other structures in the otic capsule, 1) the anterior part of the tympanic portion of the facial canal is located superolateral or lateral to the cochlear otic capsule, 2) the posterior part of the tympanic portion is located inferior to the otic capsule of the lateral semicircular canal, and 3) the canal is located lateral to the otic capsule of the posterior semicircular canal at the second genu to the mastoid portion. It may be noticed that each aspect of the facial canal on which dehiscence is most likely is located on the opposite side of the facial canal from the otic capsule. Reichert's cartilage is thought to constitute the side of the facial canal opposite to the sulcus of the otic capsule.[9] Thus, each aspect of the canal just mentioned is the area that is completed (closed) in cooperation with Reichert's cartilage. These observations lead us to speculate that minute discordance of Reichert's cartilage with the otic capsule when completing the facial canal might be one cause of the dehiscence in these areas. It is interesting to note that the highest incidence of facial nerve dehiscence is in the oval window area, in which many derivatives of Reichert's cartilage (superstructure of the stapes, pyramidal eminence, etc) are located.

The age-related variability in the incidence of facial canal dehiscence seems to fit well with these observations. Dietzel[16] reported a higher incidence of facial canal dehiscence in infants and children 5 to 14 years old, but he did not mention noting a higher incidence in the geriatric population. The fact that ossification of the facial canal usually continues until the end of the first year of life[9] may be one reason for the high incidence of facial canal dehiscence in the fetal and newborn periods; this might also, in combination with the immunologic immaturity of this period, account for the comparatively high incidence of facial nerve paralysis due to acute otitis media in infancy and early childhood.[17] On the other hand, facial canal dehiscence has also been reported to be seen more often in ears with good pneumatization than in those with poor pneumatization.[5,6] This leads us to speculate that even in the same individual, the condition of the facial canal might change with age; a new dehiscence might appear as pneumatization progresses, even if the canal was completely closed early in life. Although mastoid pneumatization has been reported to be completed around 5 to 10 years of age,[18] we believe it is also reasonable that air cell development may continue until old age.[19] In fact, Goto[20] reported that histologically, mastoid pneumatization in terms of bone formation and resorption can be noted into old age, although radiographic observation shows that the pneumatized space appears to stop increasing in size around adolescence. These findings do not appear to contradict the results of the present study, which show that the incidence of dehiscence again tends to increase in later years after reaching its lowest point in younger individuals.

Our computer-aided 3-D reconstruction and measurement method permitted precise delineation of the shape and dimensions (not only the length, but also the width and surface area) of the dehiscences. Thus, our method was able to confirm partially both Morikawa's report[1] that dehiscences are irregularly shaped in most cases, and the reports of Hough[3] and Kaplan[4] that dehiscences are usually oval. In fact, as shown by our study, dehiscences in the oval window area are usually oval, but dehiscences identified in other anatomic sites are irregular in shape. Regarding the dimensions of dehiscences, there have been several reports in the literature on the length of dehiscences,[1,6,7,9] but no reports on the width or surface area. Baxter[7] reported the most detailed data on the length of dehiscences in each area of the facial canal; the means reported were slightly lower than ours, except for dehiscences in the cochleariform process area. This discrepancy may have resulted from a difference in measurement between the two-dimensional and 3-D techniques.

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IMMUNOHISTOCHEMICAL ANALYSIS OF THE CYTOKERATIN EXPRESSION IN MIDDLE EAR CHOLESTEATOMA AND RELATED EPITHELIAL TISSUES

DANIËL BROEKAERT, PHD
GHENT, BELGIUM

PAUL COUCKE, PHD
GHENT, BELGIUM

SABINE LEPERQUE, MD
GHENT, BELGIUM

FRANS RAMAEKERS, PHD
NIJMEGEN, THE NETHERLANDS

GOOS VAN MUIJEN, PHD
NIJMEGEN, THE NETHERLANDS

DIRK BOEDTS, MD
ANTWERP, BELGIUM

IRENE LEIGH, MD
LONDON, ENGLAND

BIRGITTE LANE, PHD
SOUTH MIMMS, ENGLAND

Immunohistochemical investigations were carried out to determine the pattern of cytokeratin (CK) expression in middle ear cholesteatoma and related epithelia. Using monoclonal antibodies specific for CK chains and the indirect immunoperoxidase technique, we examined 10 CK polypeptides for expression. The external stratified squamous epithelium of the tympanic membrane generally expressed CKs 5, 10, and 14. In addition, basal keratinocytes in the annular region of the pars tensa expressed CK 19 (a simple epithelium marker), while suprabasally the hyperproliferative marker CK 16 was expressed. These data reflect the unusual proliferative nature of this region. The unexpected appearance of CK 16 (known to have a limited distribution in healthy epidermis) clearly relates to its expression in the neighboring deep meatus. The medial simple epithelium of the eardrum revealed mucosal CKs 7, 8, 14, 18, and 19. Acquired cholesteatoma lesions, besides CKs 5, 10, and 14, consistently expressed CK 16 in suprabasal layers. These results constitute the first direct molecular evidence for the hyperproliferative nature of the cholesteatoma matrix. Overall, our CK data suggest that aural cholesteatoma lesions and epidermal tissue in this area are related. However, they do not explain the mechanism(s) by which the eardrum or meatal epithelia might invade the middle ear cavity. Congenital cholesteatomas expressed CKs 5, 10, 14, and 16 equally. These CK data do not support the idea of a metaplastic origin from middle ear mucosa; instead, they suggest activation of an ectodermal rest in the middle ear cavity.

KEY WORDS — cytokeratin, eardrum epithelia, meatal epidermis, middle ear cholesteatoma, middle ear mucosa.

INTRODUCTION

In spite of numerous efforts to explain the presence of an expanding stratified squamous epithelium within the middle ear cavity, cholesteatoma pathogenesis is still a matter of debate, as was evident at the Second and Third International Conferences on Cholesteatoma and Mastoid Surgery.[1,2] Our intention has been to try to fill the many gaps in the knowledge of cholesteatoma pathogenesis by a fundamental approach to the differentiation of the cholesteatoma matrix. We focused our investigations on markers of soft keratinization and utilized epidermal tissues as a reference. Previously, we surveyed the behavior of the nucleus,[3,4] the cross-linking of structural polypeptides,[5,6] and the role played by epidermal transglutaminase.[7,8] These studies showed that cholesteatoma manifests a keratinization of the epidermal type, although the balance of early versus late stages of keratinization is altered in favor of the early ones. In addition, terminal keratinization is defective as far as cross-linking near the cellular membrane is concerned.

Recently, we also reported on the cytokeratin (CK) and vimentin expression in acquired middle ear cholesteatoma lesions.[9] The CKs are prominent differentiation markers in epithelial cells, constituting in humans a complex family of 19 closely related polypeptides subject to differential (co)expression.[10] The composition of the CK subsets depends on the epithelial type and location, the cell type, and the differentiation state reached in stratified epithelia.[11] In pathologic conditions, the expression rules are equally valid.[11] As applied to the cholesteatoma project, we determined that the CK profile in the matrix is of the epidermal type, although we found some expression of nonepidermal CKs. Probing both the early and late phases of differentiation, we again found certain alterations suggesting a hyperproliferative disease.[9] In the meantime, this work has been largely confirmed by parallel studies.[12,13]

From the Laboratory of Physiological Chemistry (Broekaert, Coucke) and the Department of Otorhinolaryngology (Leperque), State University of Ghent, Ghent, and the Department of Otorhinolaryngology (Boedts), University of Antwerp, Antwerp, Belgium; the Department of Pathology, Nijmegen University Hospital, Nijmegen, the Netherlands (Ramaekers, Van Muijen); and the Skin Tumour Laboratory, The London Hospital, London (Leigh), and The Imperial Cancer Research Fund, Clare Hall Laboratories, South Mimms (Lane), England. This study was partially supported by the Belgian Nationaal Fonds Wetenschappelijk Onderzoek.

REPRINTS — Daniël Broekaert, PhD, Laboratory of Physiological Chemistry, Faculty of Medicine, KL Ledeganckstraat 35, B-9000 Ghent, Belgium.

The primary purpose of the present study was to extend our observations to the outer epidermal layer and to the inner simple epithelium of the eardrum, in which we have systematically looked for differences in the CK expression between the various anatomic regions. These regions have a distinct ultrastructural morphology[14] and present a different frequency of perforations, leading to various clinical forms of cholesteatoma, perhaps mediated by different etiologic factors.[1,2] Second, we have been able to reconstruct the CK expression throughout the meatus, since skin autopsy specimens from precisely circumscribed sites were available. Third, the availability of new antibodies justified an additional screening of tissues for expression of some CK polypeptides that were beyond the scope of our previous investigations.[9] Among these is CK 16, a major CK polypeptide in hyperproliferative conditions.[11] Finally, for the first time we included a small group of primary or congenital cholesteatomas. The etiology of these lesions concentrates on the activation of an embryonic or ectodermal rest in the middle ear cleft. Those who reject a congenital origin refer to metaplasia of middle ear mucosa due to inflammation.[1,2]

MATERIALS AND METHODS

Materials. Biopsy sampling from reference epidermal tissues, middle ear mucosa, and acquired cholesteatomas was exactly as described before.[9] Full-thickness sheets of skin were dissected at regular distances from the bony and cartilaginous parts of the canal. Congenital cholesteatomas were screened with the utmost strictness and were obtained from children with a perfectly normal eardrum and without any previous otitis media or history of prior middle ear disease. All biopsy specimens stored in liquid nitrogen were processed for cryosectioning (5 μm) at the appropriate time.

Intact tympanic membranes (TMs) were dissected from cadavers (normal adults, both ears, 1 to 2 hours postmortem) by means of appropriate microsurgical instruments. A circumferential incision was made about 5 mm from the annulus, the annulus was lifted, and the whole TM and cuff of the adherent canal skin was removed with the malleus handle. Following rinsing with Hanks' balanced salt solution, the whole TM and adjacent meatal skin were prepared carefully under a binocular microscope. Subsequently, these specimens were stored temporarily in liquid nitrogen. Afterward, transverse cryosections (5 μm) were cut serially throughout the TM, providing at least 6 and at most 10 levels for close inspection.

Immunohistochemical Staining. For most parts of the study, frozen sections were processed for the indirect immunoperoxidase technique by using murine monoclonal antibodies. Air-dried cryosections (2 hours, 20°C), fixed in acetone for 10 minutes at 20°C, were rehydrated for 5 minutes in 10 mmol/L phosphate buffer, pH 7.2, containing 0.85% sodium chloride (PBS). Monoclonal antibodies were applied, either undiluted or diluted (1/5, 1/10, or 1/25 in PBS) for 30 minutes at 20°C in a moist chamber. Only LH8, 21D7, KK8.60, KS8.12, KS8.58, PAB601, and LL026 were applied as an undiluted culture supernatant or were diluted 1/2 in PBS. Tissue culture medium from nonproducing hybridomas was used as a negative control. Subsequently, slides were washed in PBS (jet clean followed by three washes, 10 minutes each, using a magnetic stirrer, the second wash containing in addition 0.1% Tween-20). Rabbit anti mouse immunoglobulin (Ig) conjugated to peroxidase (1/40, respectively, in 10% normal human serum in PBS) was used as a second antibody (30 minutes at 20°C). Probing for CK 5 by the rat monoclonal antibody 21D7 required the rabbit anti rat Ig peroxidase conjugate (1/40, respectively, in PBS enriched with 10% normal human serum) as a second antibody. The sections were washed for another 30 minutes as described above, except that 0.05 mol/L sodium acetate buffer, pH 4.85, was substituted for the third wash. 3-Amino-9-ethylcarbazole (0.2 mg/mL AB containing 0.01% hydrogen peroxide) was applied as the electron donor substrate for 5 to 10 minutes. Finally, sections were washed in running tap water, counterstained with Mayer's hematoxylin (15 to 30 seconds), and mounted in Kaiser's glycerin-gelatin (Merck No. 9242).

A minor number of sections were stained by the indirect immunofluorescence method. In this method, 0.1% Tween-20 and 100 mmol/L potassium chloride in PBS was applied in the first wash, and rabbit anti mouse Ig conjugated to fluorescein or rhodamine (1/20 in 10% normal human serum in PBS) was used as the second antibody. Slides mounted in PBS-glycerin (1/1) were viewed with a Dialux 20 microscope (Leitz, Wetzlar, Germany) equipped with a Ploemopak epi-illuminator (type 2.4) and the appropriate filter blocks for fluorescein (I2) and rhodamine (N2). All secondary antibody conjugates were purchased from Nordic Immunological Laboratories (Tilburg, the Netherlands).

Two panels of monoclonal antibodies were applied to the serial sections. The first panel (Table 1[10,15-24]) was applied to only meatal tissues, TM (5 samples), and congenital cholesteatomas (5 samples) to complete our earlier investigations.[9] The second panel (Table 2[10,25-28]) was used here for the first time on primary and acquired cholesteatomas (5 and 12

TABLE 1. FIRST MONOCLONAL ANTIBODY PANEL

Antibody	*Corresponding Antigen(s)**	*References*
6B10	CK 4	15
RCK102	CKs 5 and 8	16
RCK105	CK 7	17, 18
LE41	CK 8	19
RKSE60	CK 10	20
LPH1	CK 10	Unpublished data
LH3	CK 10	21
1C7	CK 13	15
2D7	CK 13	15
LH8	CK 14	Unpublished data
M9	CK 18	Unpublished data§
RCK106	CK 18	17, 18
RGE53	CK 18	22
CK18-2	CK 18	16
LE61	CK 18	19
LP2K	CK 19	Unpublished data¥
Clone 80	Broad-spectrum CKs	23
RCK103	CK 5†	18
Vim9	Vimentin	24
RV202	Vimentin	18
RD301	Desmin	17

*Numbered according to catalog.[10]

†Broad-spectrum CKs including CK 5, and neurofilament polypeptides.

§Commercially available from Sanbio BV (Uden, the Netherlands).

¥Commercially available from Amersham (England).

TABLE 2. SECOND MONOCLONAL ANTIBODY PANEL

Antibody	*Corresponding Antigen(s)**	*References*
21D7†	CK 5	Unpublished data
M20	CK 8	25
LPH2	CK 10	26
Kk8.60	CKs 10 and 11	27
Ks8.12	CKs 13 and 16	27
Ks8.58	CKs 13 and 16	28
PAB601	CK 14	26
LL026	CK 16	Unpublished data
LP34	Panepidermal CKs	26

*Numbered according to catalog.[10]

†Rat monoclonal antibody.

samples, respectively) and all related and reference tissues.

Overall, 10 CK polypeptides were screened individually. To overcome false-negative results due to masking effects, repetitive screening of CKs 5, 8, 10, 13, 14, and 18 was performed by applying antibodies with different specificities. To detect potentially positive sites, nonspecific probes were used. Vimentin probes highlighted tissues of mesenchymal origin.

RESULTS

In this section, only positive data are described. Broad-spectrum (nonspecific) probes (clone 80, RCK103, and LP34) provided uniform staining of meatal epidermis, lateral stratified squamous and medial simple epithelia of the TM, middle ear mucosa, and cholesteatoma. The CK data are summarized in Table 3.[9]

Meatal Epidermis. Whether samples originated from deep in the canal (ie, near the annulus) or from more external sites, the presence of CKs 5, 10, and 14 was consistently demonstrated. The CK 5 and 14 staining was moderate in intensity and localized mainly in basal keratinocytes; it faded away in the suprabasal layers. In contrast, CK 10 staining was intense in the suprabasal layers. Kk8.60, specific for CKs 10 and 11, gave similar staining profiles. Unexpectedly, the meatal epidermis exhibited weak to intense CK 16 staining, restricted to the suprabasal keratinocytes in TM-associated regions (Fig 1A).

TABLE 3. SURVEY OF IMMUNOHISTOCHEMICAL CYTOKERATIN DATA

	Meatal Epidermis	*Tympanic Membrane* *Lateral Side*	 *Medial Side*	*Middle Ear Mucosa*[a]	*Acquired*[a] *Cholesteatoma*	*Congenital Matrix*
CK 4	–	–	±[b]	+	±[c]	–
CK 5	+	+	–	–	+	+
CK 7	–	–	+	+	±[c]	–
CK 8	–	–	+	+	±[c]	–
CK 10	+	+	–	–	+	+
CK 13	–	–	±[b]	–	±[c]	–
CK 14	+	+	+	+	+	+
CK 16	±[d]	+[e]	–	–	+	+
CK 18	–	–	+	+	±[c]	–
CK 19	±[f]	±[f]	+	+	±[c]	–

[a] Combined data from previous paper[9] and present investigations.

[b] Expressed in pseudostratified epithelial foci.

[c] Focal staining, associated with terminal keratinization in certain cases.

[d] Staining restricted to deep meatus.

[e] Extremely weak staining in central areas, markedly intensified in annular regions.

[f] Staining of basal keratinocytes in annular regions of lower part of tympanic membrane.

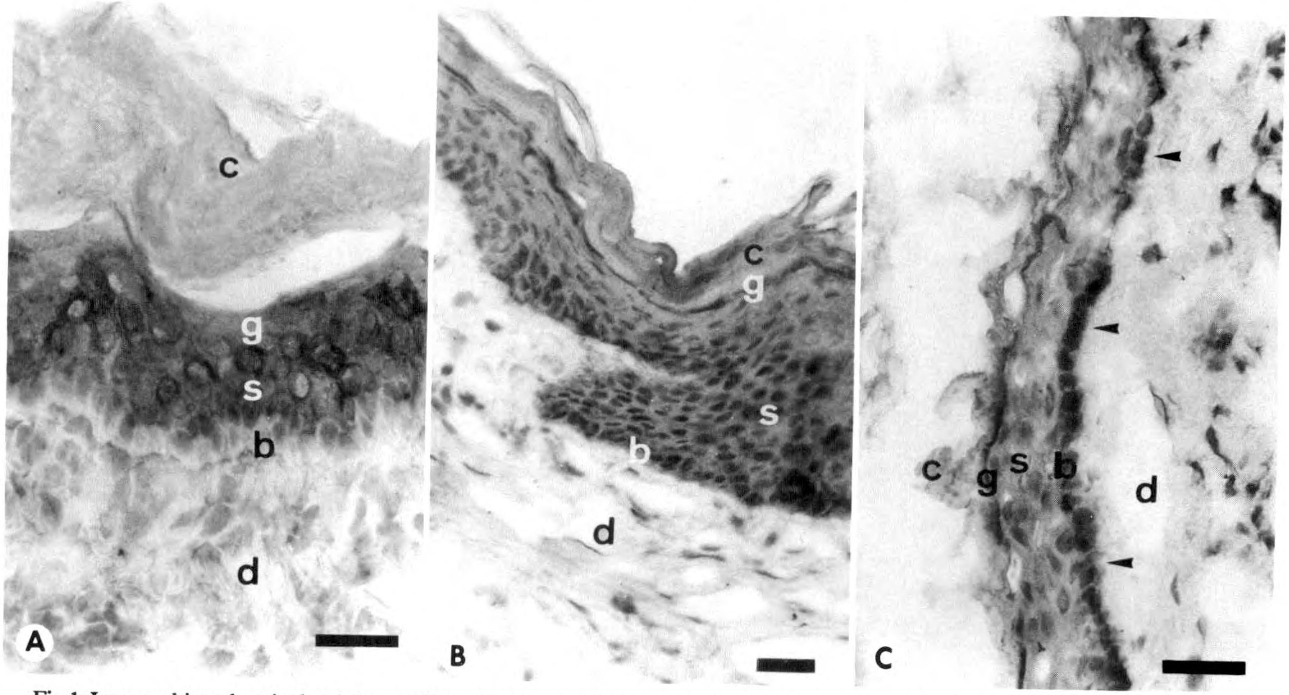

Fig 1. Immunohistochemical staining profiles of deep meatal epidermis. Tissue slices were routinely counterstained with Mayer's hematoxylin. b — stratum basale, c — stratum corneum, d — dermis, g — stratum granulosum, s — stratum spinosum, bars — 30 μm. A) Distinctive LL026 staining, indicating presence of cytokeratin (CK) 16 in suprabasal layers. B) Significant Ks8.58 staining of malpighian layer, indicating expression of common determinant of CKs 13 and 16. C) Presence of CK 19 in basal keratinocytes of annulus, confronting region neighboring pars tensa (LP2K staining). Arrowheads — cells with maximal staining intensity.

This unusual expression of CK 16 was observed in deep canal samples from cholesteatoma patients and from normal controls. In the other regions of the meatus, CK 16 staining was limited to the external root sheath of the hair follicles. Ks8.12 and Ks8.58, both specific for CKs 13 and 16, yielded a significant staining of basal keratinocytes. Sometimes this staining extended throughout the malpighian layer (Fig 1B). We also observed the presence of CK 19 in basal keratinocytes of annulus-associated regions opposite the pars tensa (Fig 1C).

A specific search for CKs 16 and 19 in the interfollicular epidermal regions (eg, breast, abdomen, shoulder, arm, and retroauricular area) yielded no positive staining, except for CK 19 in scanty Merkel's cells. Thick epidermal tissues from pressure-sensitive sites (eg, thumb, sole, heel), however, consistently yielded weak to moderately intense CK 16 staining, visible suprabasally in the living layers.

Finally, vimentin reactivity was present exclusively in Langerhans' cells, spread among keratinocytes.

Tympanic Membrane. The lateral stratified squamous epithelium clearly displayed a CK pattern characteristic of epidermal tissue. As a rule, staining profiles were similar throughout the pars flaccida, the pars tensa, and the annular regions. The CK 5 antibody 21D7 provided weak labeling of both living and dead layers. Alternatively, the RCK102 staining of CK 5 in the absence of CK 8 was maximally intense in basal keratinocytes, and minimal in final keratinization areas. Cytokeratin 10 was a prominent marker of all suprabasal stages, and Kk8.60 produced a similar staining profile. Cytokeratin 14 staining was weak and restricted to the deeper layers.

Throughout the TM, from the umbo to the annulus, we observed weak LL026 staining, suggesting a minor suprabasal expression of CK 16. Near the annulus, however, the staining increased, clearly indicating CK 16 in suprabasal keratinocytes (Fig 2A). Cytokeratin 19 was present in basal keratinocytes in the annular region bordering the pars tensa. Significant labeling produced by Ks8.12 and Ks8.58, indicative of CK 13 and/or CK 16, was observed throughout epithelial layers at all sites (Fig 2B). Finally, staining for vimentin revealed very few Langerhans' cells, except near the annulus.

The epithelium lining the medial side (in central areas), and adjacent to the mucosal lining of the tympanic cavity, significantly expressed CKs 7, 8, (M20-positive although LE41-negative), 14 (LH8-positive, PAB601-nonreactive), 18, and 19. Rare pseudostratified columnar foci expressed CKs 4 and/or 13. RCK102 provided uniform staining, while Ks8.12 and Ks8.58 staining was restricted to columnar cells, leaving squamous cells unstained.

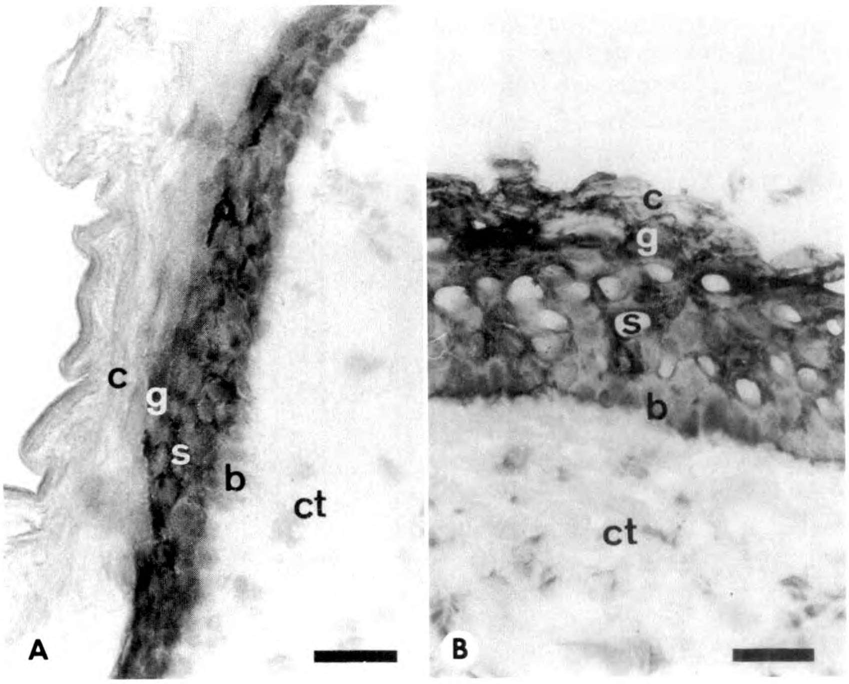

Fig 2. Immunohistochemical staining profiles of lateral stratified squamous epithelium of tympanic membrane. Tissue slices were routinely counterstained with Mayer's hematoxylin. ct — connective tissue, bars — 30 μm. Other abbreviations as in Fig 1. A) Expression of CK 16 in suprabasal layers near annulus (LL026 staining). B) Significant Ks8.12 labeling throughout all epithelial layers.

Middle Ear Mucosa. The CK reactivity in middle ear mucosa, screened with the second antibody panel (Table 2), was identical to the reactivity of the medial simple columnar epithelium of the TM; ie, only M20, Ks8.12, and Ks8.58 provided substantial staining.

Acquired Middle Ear Cholesteatoma. Using the new antibody panel (Table 2), we reconfirmed the obligatory expression of CKs 5, 10, and 14 during matrix differentiation. The antibody 21D7 weakly stained matrix tissues in all cases. Some staining extended throughout the accumulated keratinous debris (11 of 12 cases). Cytokeratin 10 staining, as a rule, was more intense and confined to the suprabasal layers. However, only the suprabasal layers in advanced stages of differentiation were stained in 8 cases. In 4 other cases, the CK 10 staining was present from the first suprabasal layer onward. Kk8.60 generated similar staining profiles. Cytokeratin 14 again was the predominant marker of the lower matrix half. Progressive loss of CK 14 characterized terminal differentiation.

The hyperproliferative marker CK 16 was consis-

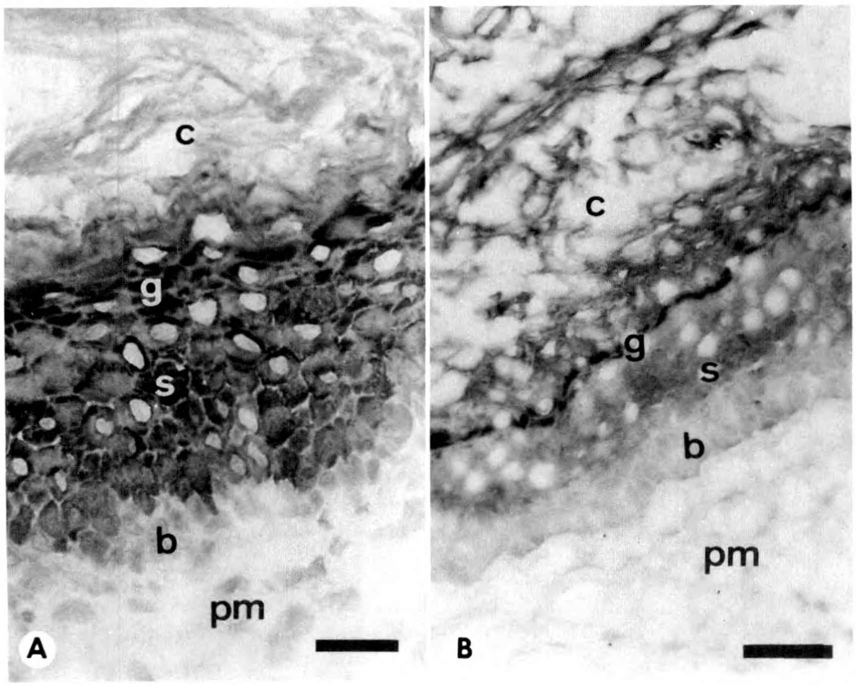

Fig 3. Immunohistochemical staining profiles of acquired middle ear cholesteatoma. Tissue slices were routinely counterstained with Mayer's hematoxylin. pm — perimatrix, bars — 30 μm. Other abbreviations as in Fig 1. A) Prominent LL026 staining of suprabasal matrix keratinocytes, indicating expression of CK 16. B) Typical Ks8.12 labeling profile, ie, diffuse minimal staining of basal keratinocytes and moderate staining of suprabasal matrix cells, completed by maximal staining of keratinous debris.

tently identified in the suprabasal matrix cells. In general, well-developed matrix configurations acquired a stronger staining than thinly stretched matrix tissues (Fig 3A). The corresponding epitope largely appeared in the adjacent stratum corneum areas in 4 of 12 cases, but was not evident in the horny layers in 8 other cases. KS8.12 and KS8.58 both provided similar staining profiles, distinct from the LL026 profile. In 6 of 12 cases basal keratinocytes showed diffuse minimal staining, while in 4 cases they revealed maximal labeling. Suprabasal cells retained a positive staining, which was most prominent in the keratinous debris (Fig 3B).

Congenital Cholesteatoma. Our preliminary data on five primary cholesteatomas indicate the presence of CKs 5, 10, and 14 in an epidermal mode, and of CK 16 exclusively in suprabasal matrix cells. In three cases, the expression of the CK 16 epitope was occasionally present in the stratum corneum. The expression of certain nonepidermal CKs, sometimes noted in acquired cholesteatoma tissues,[9] was not observed.

DISCUSSION

The present data permit discussion of the state of differentiation reached in middle ear cholesteatoma tissues.

Although the meatal epithelium provided a typical epidermal CK pattern, the deep meatus was unique. In addition to CKs 5, 10, and 14, expressed at the appropriate level of differentiation, we could see suprabasal CK 16 in healthy as well as in cholesteatoma tissue. Cytokeratin 16 has previously been identified as a molecular marker of hyperproliferative keratinocytes.[11,29] It has been observed in only a limited number of healthy epidermal sites (ie, soles and outer root sheaths of hair follicles).[10] We found CK 16 in other pressure-sensitive sites having a stiff, thickened epidermis (eg, heel and thumb). In contrast, all thin epidermal tissues, including those from the cartilaginous and lateral bony parts of the meatus, were nonreactive.

The unusual character of the boundary area of the meatus and the eardrum is further documented by the presence of CK 19, which is a major constituent of simple epithelia and to some extent of certain pseudostratified epithelia of internal organs.[10,11] Cytokeratin 19 in epidermal basal keratinocytes has never been reported and is difficult to evaluate. However, by analogy with the staining pattern seen in other stratified squamous epithelia (eg, conjunctiva),[30] CK 19 may reflect the presence of proliferating stem cells.

The lateral stratified squamous epithelium of the TM displayed an epidermal CK pattern in the pars flaccida, the pars tensa, and the annular region. A supplementary expression of CK 16 was noticed in suprabasal keratinocytes of annulus-associated regions. From there to the umbo, staining decreased. Cytokeratin 19 was invariably identified in basal keratinocytes near the inferior annular part of the TM. In summary, the edge of the TM and the deep meatus displayed identical CK profiles, indicating an obvious continuity in this transitional area.

Our CK data show unusual proliferative capacity around the annular region opposing the pars tensa. This is consistent with earlier reports of a specific area of ^{3}H-thymidine uptake and subsequent spreading.[31-35] Similar conclusions can be drawn from wound closure experiments[33,36,37] and from studies on the course of fetal and postnatal growth of the eardrum and deep canal.[38]

The CK composition of the medial simple epithelium of the eardrum, whether composed of columnar or squamous cells, is very similar to that of the middle ear mucosa, as noted in our previous study.[9] In this study, we have also collected convincing evidence that CK 8 belongs to the mucosal CK family. This finding is also supported by other current studies.[12,13] Mucosal CK (in addition to CK 14) is composed primarily of typical simple epithelial CKs, ie, CKs 7, 8, 18, and 19, and conforms to rules of CK expression.[11] As a consequence, the question of whether CK 5 is expressed in middle ear mucosa, which was indirectly postulated in the past,[9] is now open for discussion. We obtained negative results with the 21D7 antibody, although CK 14, the natural coexpression partner of CK 5, is present. Finally, we observed CK 4, a marker of nonepidermal stratified epithelia,[11] in mucosa in our earlier study,[9] but actual data show CK 4 only in pseudostratified foci on the medial side of the TM.

Concerning primary and acquired cholesteatomas, we confirmed our previous conclusions that CKs 5, 10, and 14 are expressed in an epidermal mode.[9] Additionally, CK 16 was observed suprabasally in matrix tissues. Since CK 16 is a marker for hyperproliferative keratinocytes in general,[11,29] this observation provides direct biochemical evidence for the hyperproliferative nature of cholesteatoma. This hyperproliferative state, whether focal, local, or general, has been postulated before, but evidence was only circumstantial.[9] Here again, the expression of the advanced phenotypic keratinization marker CK 10 was slightly delayed, underscoring the hyperproliferative characteristic. Expression of nonepidermal

CKs was not observed in our small group of congenital lesions, contrary to reported experience with acquired lesions.[9,12,13] This difference suggests that congenital cholesteatomas might evolve, more strictly than acquired lesions, through the soft keratinization route. The Ks8.12 and Ks8.58 staining profiles, representing a common epitope of CKs 13 and 16, were wider than the CK 16 patterns shown by LL026, although CK 13 apparently was absent from the CK complement. According to the CK expression rules and the actual tissue staining distribution, we presume that CK 15, in addition to CKs 13 and 16, was recognized by both antibodies.[27]

The functional significance of human CKs is conserved under pathologic conditions.[11,39] Thus, CK typing has predictive value in identifying pathologic states. In acquired cholesteatoma, the striking similarity between the CK complement in the matrix and in the epidermal tissues (deep meatus and/or lateral cover of the TM) suggests a pathogenetic link. Our immunohistochemical investigations do not explain the mechanism(s) by which the eardrum or meatal epithelium might invade the middle ear cavity. The CK profiles obtained do not support the metaplastic origin of middle ear cholesteatoma, however. In the case of a stratified squamous metaplastic lesion, a unique combination of one or more of the major CKs from the recipient tissue and stratification-related CKs has been reported.[40,41] When the metaplasia, in addition, exhibits phenotypic keratinization including cornification, expression of terminal epidermal keratinization markers is expected. Our study demonstrates that the cholesteatoma CK complement does not have this metaplastic characteristic. Although this does not disprove the metaplasia theory, neither does it provide support for it.

A metaplastic origin of congenital cholesteatomas, likewise, is unsupported by our data. Instead of metaplasia, our data support the activation and expansion into a lesion of an embryonic or ectodermal rest in the middle ear itself. The existence of these islands is discussed in detail elsewhere.[42]

ACKNOWLEDGMENTS — This paper is dedicated to the memory of Prof J. Marquet, deceased March 18, 1991, at age 63. We recognize with appreciation Prof Marquet for his guidance, continued interest, and stimulation. This support will be sorely missed. We salute Prof Marquet for his enormous contribution to clinical and investigative otorhinolaryngology. The authors thank A. Huysmans, O. Moesker, and G. Schaart for assistance in antibody preparation, B. Geiger for his generous gifts of KS8.12, KS8.58, and KK8.60, and F. Colardyn for use of facilities for autopsy. M. Esquenet and M. Davey are acknowledged for reading the manuscript.

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SKULL BASE DUMBBELL TUMOR: SURGICAL EXPERIENCE WITH TWO ADOLESCENTS

ROLAND D. EAVEY, MD
PARVIZ JANFAZA, MD
PAUL H. CHAPMAN, MD
BROOKE SWEARINGEN, MD
NORBERT LIEBSCH, MD
ALFRED WEBER, MD
KENNETH R. DAVIS, MD
WILLIAM S. FERGUSON, MD
BOSTON, MASSACHUSETTS

Pediatric skull base tumors are rare and until recently were considered unresectable. We present two patients with tumors of similar anatomic position with an extracranial component in the infratemporal fossa and parapharyngeal space, an isthmus at the foramen ovale, and a superior component in the middle cranial fossa in the region of the cavernous sinus. A 15-year-old girl experienced contiguous spread of a spindle cell sarcoma; an 18-year-old boy developed a chondrosarcoma. A middle fossa approach provided the advantage of surgical avoidance of structures such as the middle ear and mastoid, facial nerve, and mandible. Postoperative recovery was rapid. Our impression is that preoperative carotid artery occlusion and a middle fossa approach for tumor resection can be performed in a young patient with acceptable morbidity and at least short-term benefit. Surgery can, therefore, provide an additional therapeutic approach to complement irradiation and chemotherapy.

KEY WORDS — chondrosarcoma, middle fossa approach, pediatric skull base tumor, skull base dumbbell tumor, skull base surgery, spindle cell sarcoma.

INTRODUCTION

Skull base surgery offers the intriguing opportunity to perhaps benefit patients who have lesions previously considered to be unresectable. Difficult areas such as the cavernous sinus,[1] petrous apex,[2] and infratemporal fossa[3] can be surgically approached with relative safety.

Tumors of the skull base in children and adolescents are quite rare. Those few tumors found have presented with a variety of tissue types and separate skull base anatomic locations.[4] Therefore, experience with specific skull base tumors in pediatric patients is limited, and customized management must be employed. This invites the question of whether surgical debulking or excision of such a tumor might be offered for a young patient.

We report our experience with two patients who had similarly located dumbbell-shape tumors, in the middle fossa–cavernous sinus region and the infratemporal fossa and parapharyngeal space, to add to the cumulative experience in the literature.

CASE 1

A 12-year-old girl presented in 1984 with a 2-month history of left cheek and ear pain that was discovered to be due to a left parapharyngeal space spindle cell sarcoma. She was treated with irradiation twice daily at 3,360 cGy and received vincristine sulfate, actinomycin D, and cyclophosphamide. She also underwent resection of the tumor via a left mandibular body split approach with total gross excision to the skull base.

She returned in 1987 with a "funny sensation" along the distribution of left cranial nerves V1 and V2 and complained of diplopia. Her physical examination revealed no obvious evidence of tumor. A computed tomography (CT) scan (Fig 1) revealed a new mass measuring 3.5 cm in vertical height. The extracranial component of this mass was in the area of the lateral pterygoid muscle and plate and extended medially and posteriorly to the lateral wall of the pharynx. This mass superiorly widened the foramen ovale and continued into the middle cranial fossa, where medially it abutted the cavernous sinus and posteriorly it protruded into the prepontine cistern.

The patient underwent an awake, subzygomatic arch percutaneous needle biopsy of the left infratemporal fossa mass using CT guidance. Cytologic examination was positive for high-grade sarcoma. A magnetic resonance imaging (MRI) scan corroborated the CT findings and demonstrated a possible plane between the tumor and the temporal lobe (Fig 2). The carotid artery in the cavernous sinus appeared

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From the Departments of Otolaryngology (Eavey, Janfaza) and Radiology (Weber), The Massachusetts Eye and Ear Infirmary, and the Departments of Neurosurgery (Chapman, Swearingen), Radiation Medicine (Liebsch), Radiology (Davis), and Pediatrics (Ferguson), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

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REPRINTS — Roland D. Eavey, MD, Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

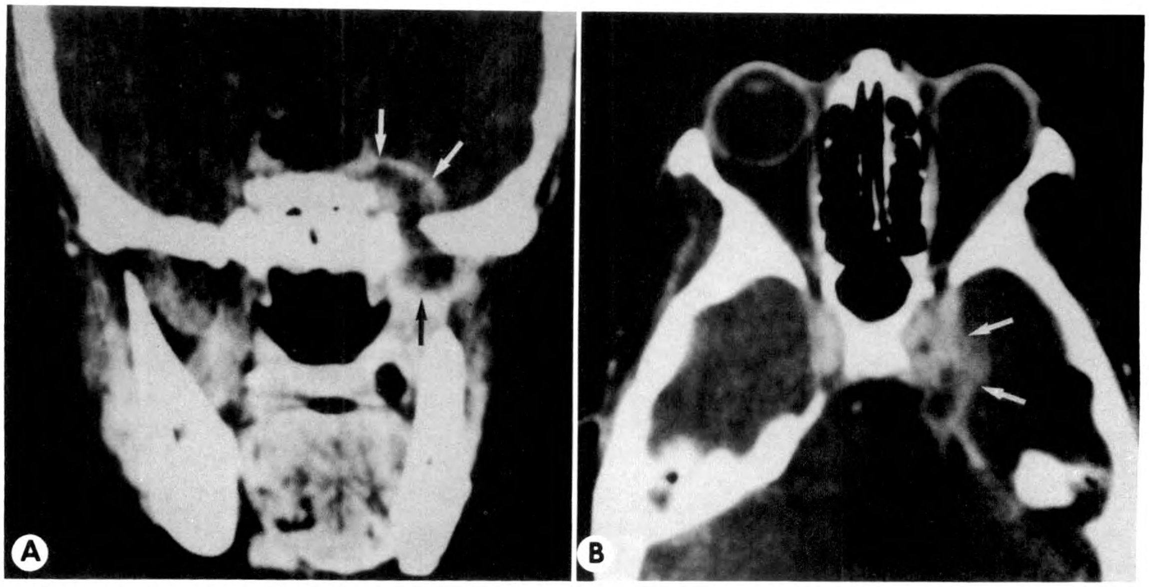

Fig 1. (Case 1) Computed tomograms. A) Coronal section demonstrating dumbbell-shape tumor (arrows). Isthmus is widened foramen ovale. B) Axial section demonstrating tumor (arrows) in region of cavernous sinus.

to be patent. An arteriogram demonstrated flow through the carotid without definite evidence of tumor invasion. Since surgery had been elected, balloon embolization of the internal carotid artery was performed both distal and proximal to the tumor in the cavernous sinus after an occlusion test was performed to elicit possible neurologic symptoms.

The patient was taken to the operating room, where she underwent a left-sided middle cranial fossa approach (Fig 3). The cranial bone flap was opened and the temporal lobe was elevated sufficiently to see an obvious tumor with dense adherence to the dura, although appearing to be clearly defined by a plane of separation from the temporal lobe (Fig 4A). The tumor was adherent in the region of the cavernous sinus; the intracavernous carotid artery wall was found to be involved and was opened. A previously placed occlusion balloon was exposed in this arterial fenestration; no bleeding occurred (Fig 4B). Following complete, gross intracranial tumor removal, the residual tumor involving the foramen ovale, the third division of the fifth cranial nerve, and the infratemporal fossa was approached through the same exposure. The tumor was able to be followed through the foramen ovale into the left infratemporal fossa, where it was dissected from surrounding tissue by blunt and ultrasonic dissection through the eustachian tube and into the nasopharynx (Fig 4C). At this point, the radiotherapy team provided the previously constructed implant of radioactive iodine 125 seeds embedded in Gelfoam. Abdominal fat was placed medially against the clivus, onto which the implant was laid. The temporalis muscle was sutured to the dura of the cavernous sinus to provide a new support for the temporal lobe and to help provide a watertight seal.

The next morning the patient was alert; she demonstrated a total third cranial nerve palsy. She rapidly became ambulatory and was able to go home at 1 week postoperatively. A repeat CT scan demonstrated absence of tumor; the radioactive iodine seeds were noted (Fig 5).

The patient continued treatments with supplemental external beam irradiation and also with chemotherapy. Six months later she underwent a craniotomy for a metastasis to the peripheral dura just under the skull table, quite distant from the original lesion. During this interval, the patient had experienced a return of most eye function from the third, fourth, and sixth cranial nerves. The patient then had another fruitful symptom-free interval, in which she produced award-winning artwork, until massive intracranial recurrence was detected. A course of cisplatin dramatically but temporarily improved the lesion as seen on imaging. Thirteen months after her skull base resection, however, she slipped into a coma and died.

CASE 2

An 18-year-old boy presented with a 3- to 4-year history of persistent right-sided serous otitis media, previously treated twice with a pressure equalization tube. He had experienced a 2- to 3-month history of right periorbital and retroorbital headaches associated with nausea and vomiting. A CT scan demonstrated a large, partly calcified mass in the right side of the skull base. Biopsy of the nasopharyngeal component yielded findings consistent with low-grade chondrosarcoma.

The patient was referred to the Massachusetts General Hospital Department of Radiation Medicine

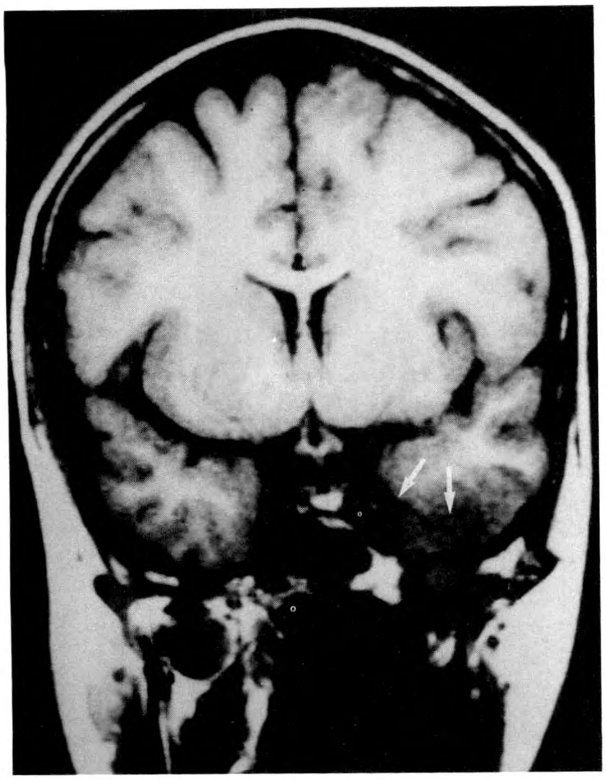

Fig 2. (Case 1) Magnetic resonance image demonstrating potential plane between tumor and temporal lobe (arrows). Carotid artery appears patent.

in 1989 for consideration of treatment with proton beam radiotherapy. An MRI scan demonstrated a 2- to 3-cm dumbbell-shape mass in the right nasopharynx and juxtasellar region (Fig 6). The right cavernous sinus was involved by the mass, with tumor compressing the right internal carotid artery. Because of the size of the tumor, the radiation therapist felt that debulking or excision could perhaps provide the patient with a better chance for control or cure. Therefore, the patient was referred to the otolaryngology and neurosurgery services.

On physical examination, the right tympanic membrane was amber, retracted, and immobile. The left tympanic membrane was normal. In the nasopharynx, there was a mucosal-covered fullness on the right side that was somewhat erythematous as viewed with a flexible scope but appeared blue by mirror examination. Eye examination revealed a mild ptosis on the right side with limited upward and lateral gaze. There was mild hypalgesia on the right side of the nose and cheek.

Prior to a surgical procedure, the patient underwent carotid arteriography that demonstrated that the internal carotid artery was grossly obstructed by tumor just beyond the carotid bifurcation in the neck. With selective intracranial arteriography via other vessels, however, patent anastomatic tumor vascular communications were discovered that were occluded.

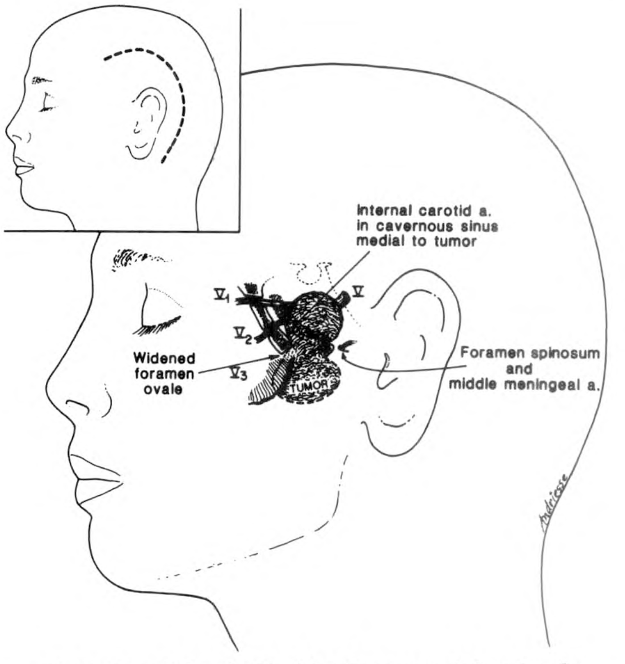
Internal carotid a. in cavernous sinus medial to tumor
V
V_1
V_2
Widened foramen ovale
V_3
TUMOR
Foramen spinosum and middle meningeal a.

Fig 3. (Case 1) Surgical incision for approach. Landmarks for tumor include foramen spinosum and foramen ovale.

At surgery, a pterional approach between the temporal and frontal lobes was used. On retraction of the temporal lobe, a large mass of tumor was noted to occupy the medial portion of the middle fossa. Because the third cranial nerve was draped over and adherent to the capsule of the tumor, an intracapsular dissection was used. The mass was very firm and cartilaginous. A frozen section demonstrated the tumor to be either well-differentiated chondrosarcoma or an enchondroma. Drilling commenced in the region of the foramen spinosum and foramen ovale, and the tumor was followed extracranially to the pterygoid. No residual tumor could be perceived. Abdominal fat was placed into the cavity. The capsule was resewn to protect the floor and prevent the temporal lobe from herniating into the resection cavity.

The next morning the patient was awake and alert and conversant. His ocular cranial nerve findings were the same as preoperatively. He was able to eat and to ambulate on the first postoperative day.

The final pathology specimen was read as a benign enchondroma. Further review was consistent with this benign diagnosis and so treatment with radiotherapy or chemotherapy was withheld.

On 3-month follow-up, the patient's vision had improved and he experienced no diplopia. On physical examination, the right ear canal was patent. There was still an apparent effusion behind the tympanic membrane. His extraocular motion was normal on inspection, as was his pupil.

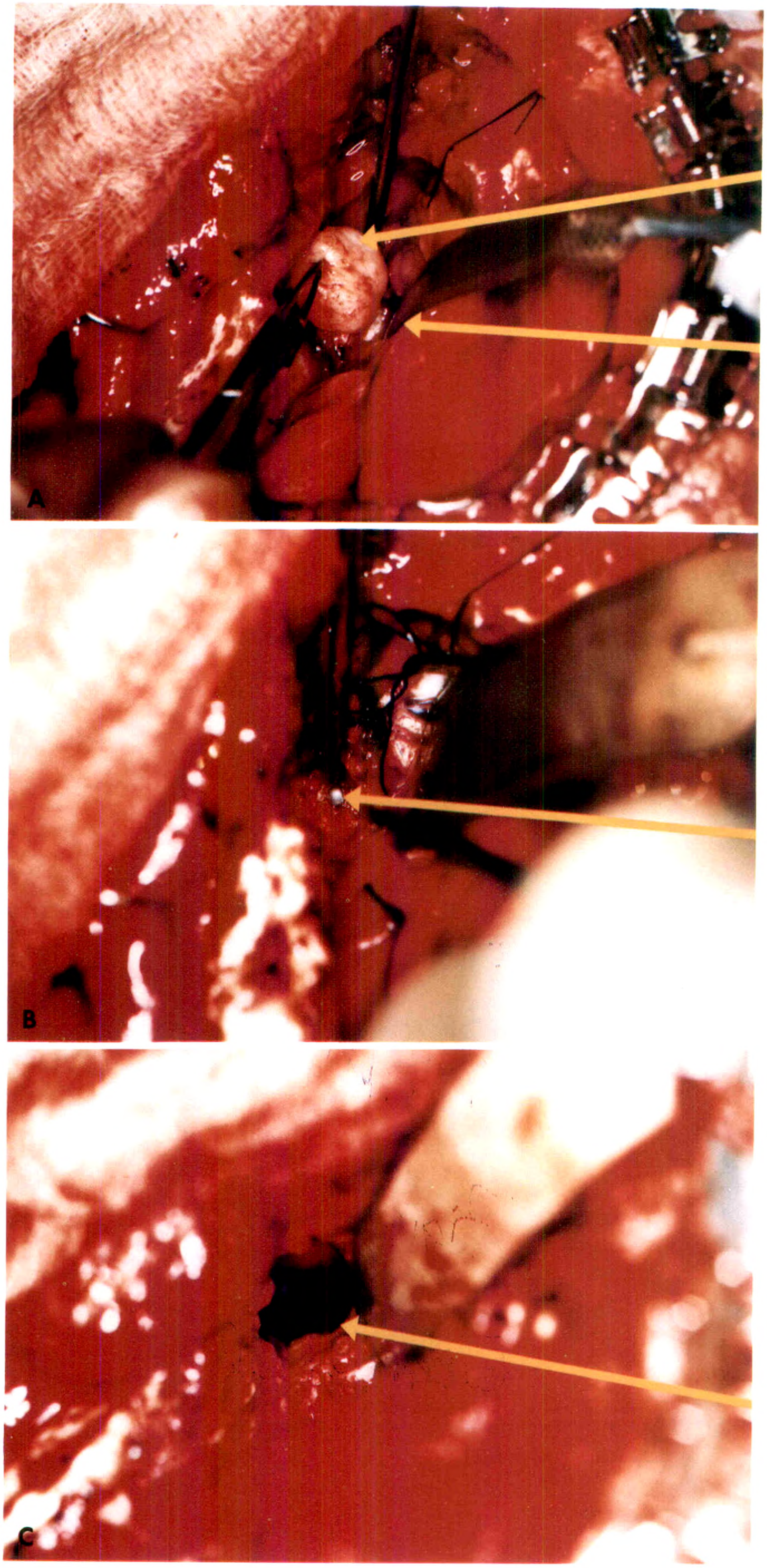

Fig 4. (Case 1) In this surgical position, caudad is to left, cephalad is to right, and anterior is to top of photo. A) Intracranial tumor (top arrow). Temporal lobe (bottom arrow) is retracted. B) Intracranial tumor removed. Note previously placed carotid artery occlusion balloon (arrow) seen through open artery wall in cavernous sinus. C) View through to nasopharynx (arrow) after tumor was resected through foramen ovale, infratemporal fossa, and parapharyngeal space.

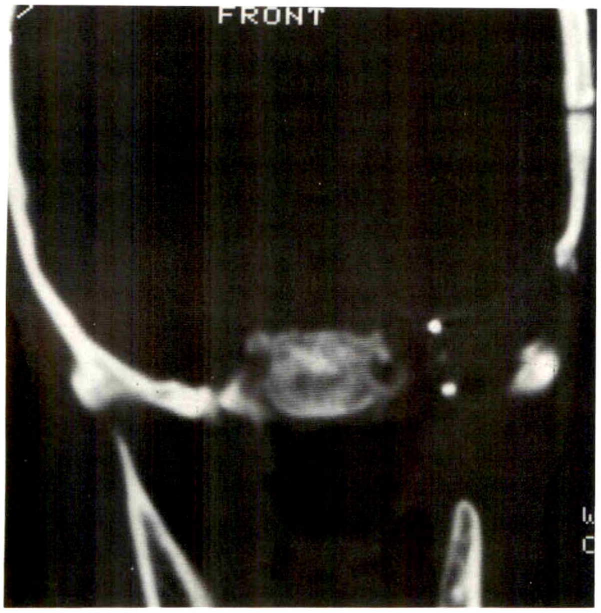

Fig 5. (Case 1) Postoperative computed tomogram. Tumor has been removed and skull base is absent. Radioactive seeds are present as small circular densities.

Eight months postoperatively the patient experienced a sudden return of retroorbital pain and diplopia. On physical examination, he demonstrated a partial fourth nerve palsy and a total sixth nerve palsy. His CT and MRI scans demonstrated an intracranial tumor mass similar to that on his preoperative films. He was again taken to the operating room and via a lateral middle fossa approach similar to that in case 1, the intracranial component was again debulked. The floor of the temporal fossa was further removed. The lateral pterygoid was exposed; tumor was encountered immediately posterior to the pterygoid. Postoperatively the patient had regained most eye motion by the fourth postoperative day, and he was discharged at 1 week. The histopathology findings were consistent with low-grade chondrosarcoma; he received proton beam irradiation and is currently alive with disease.

DISCUSSION

Skull base surgery has evolved[4,5] elegantly from the initial intrepid drainage procedures done in the preantibiotic era. For example, Brunner[6] in 1946 noted three routes to the cavernous sinus: a transsphenoid sinus approach, a middle cranial fossa approach, and Mosher's orbital exenteration–anterior approach. Masterful surgeons have refined tumor-oriented skull base surgery approaches and techniques. Such surgery, however, has been almost exclusively applied to adults. In young patients such tumors are less common, and except for angiofibroma,[7-9] surgical treatment is not standardized because of the lack of large patient series to assist with management of such lesions.

Skull base surgery should not be withheld from young patients by using age as the sole criterion of exclusion. Adolescent and pediatric patients can probably better tolerate ambitious therapy than adults. Young patients have theoretically more to gain with successful therapy, and conversely, considering the limited alternatives of palliation or no therapy, they have more to lose if treatment fails. In the case of a benign tumor causing significant symptoms, surgery becomes even more important, since no alternative treatment exists.

The rationale for debulking differs when it is used for assisting with radiotherapy as opposed to chemotherapy. For irradiation, debulking surgery can advantageously improve the tumor dosage geometry. For example, in case 2, removal of the intracranial tumor component significantly reduced the radiation dosage to the brain, especially the temporal lobe, visual pathway, and brain stem. For chemotherapy, the relevance of debulking surgery involves both downstaging of the tumor[10,11] and the fact that chemotherapy is more effective on microscopic residual tumor than on a large tumor mass. The reason may have to do with the tumor vascular supply or with cellular metabolism.

Because of the possibility of intraoperative vascular catastrophe in our cases, it was prudent to consider control in advance.[12,13] Angiographic occlusion of the carotid artery proved extremely helpful. In case 1, it was not known preoperatively that the tumor had actually invaded the wall of the carotid artery. On tumor removal, the balloon that was occluding the carotid was actually seen through a large opening in the wall of the vessel. The patient did not lose any blood; the embolization prevented a catastrophe. In case 2, embolization was helpful, since routine arteriography initially appeared to demonstrate complete tumor compression of the internal carotid artery. However, with more selective studies distal to the tumor, additional vessels were discovered that could have posed troublesome intracranial bleeding. Angiographic embolization was first tested by a trial occlusion to avoid possible neurologic sequelae. Indeed, other than some scalp sensations, patient morbidity was minimal. The long-term morbidity for a young patient such as eventual aneurysm or stroke remains unknown, but is felt to be low.

Because of the uniqueness of this type of tumor, special radiotherapy modalities were used. Besides conventional external beam irradiation, implant irradiation was performed in case 1, providing the equivalent of 10,000 cGy delivered very focally because of the short range of the emitted radiation. Another external type of radiotherapy, used for case 2, was the

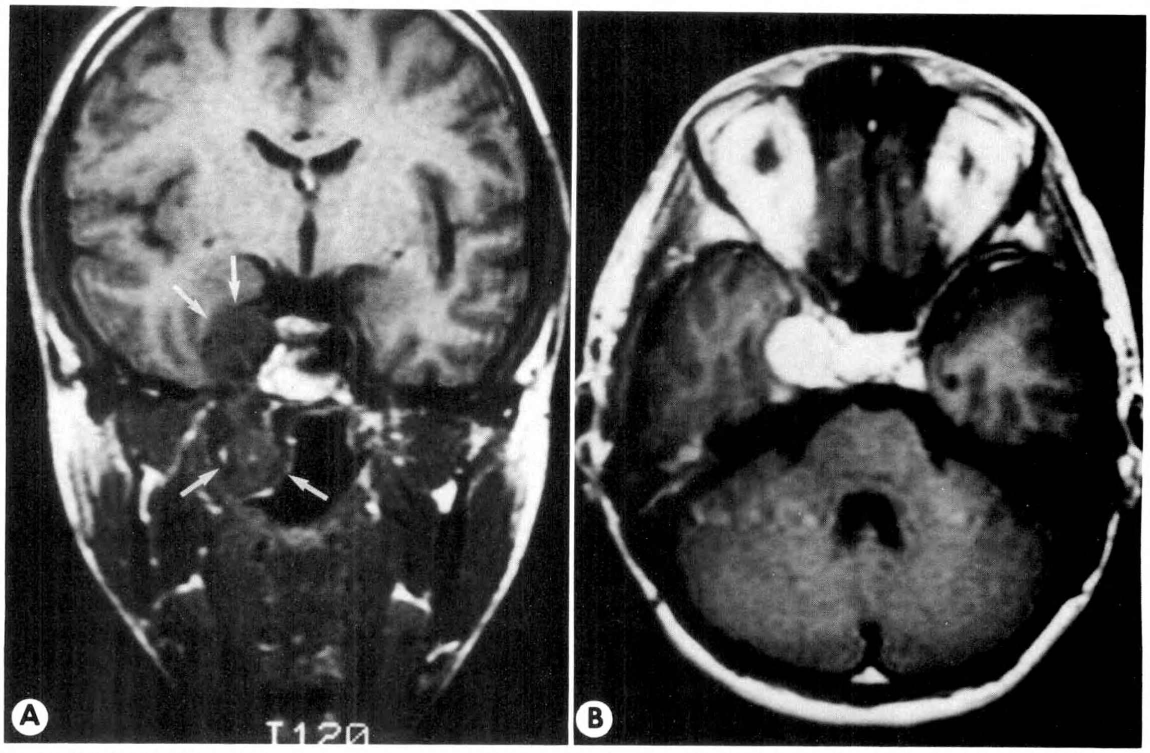

Fig 6. (Case 2) Magnetic resonance images. A) Demonstrating dumbbell-shape lesion (arrows). B) Gadolinium-enhanced, demonstrating tumor at cavernous sinus.

proton beam.[14] The physical characteristics of the proton beam and its interaction with living matter permit concentration of the radiation dose in the tumor to reduce the irradiation of surrounding critical normal tissues and organs. This technique has yielded quite satisfactory results in achieving control of certain tumors with minimal treatment-related morbidity, ie, in the management of base of skull chondrosarcoma and chordoma, in which the 5-year actuarial survival local control rate is 82% and the disease-free survival rate is 76%.[15]

The middle cranial fossa contains a high density of critical anatomic structures medially and inferiorly.[5,16] These structures include the hypothalamus and midbrain, the cavernous sinus, cranial nerves III, IV, V1, V2, V3, and VI, and the middle meningeal artery. The carotid artery courses along the floor of the middle fossa, but is well encased in the temporal bone until it appears, quite medially, in the foramen lacerum. The other important foramina are also medial: the foramen rotundum for the exit of V2, the foramen ovale for the exit of V3, and the foramen spinosum for the entry of the middle meningeal artery. Therefore, with such a medial density of structures, one approach, in theory, to a tumor of this location is from a lateral route.

The infratemporal fossa, conversely, is the reverse, with more anatomic structures located laterally and superiorly.[16] This fossa is medially bounded by less critical structures such as the lateral pterygoid plate and pharynx. Although the lateral approach to this fossa is quite refined and well described,[3] such an exposure does involve surgery of the mastoid and middle ear, facial nerve, mandible, and vascular soft tissues within the fossa. Given these anatomic realities, one logical exposure to an infratemporal fossa tumor to avoid important lateral structures is by continuation of a middle fossa approach aimed medially toward the pharynx. A similar approach in the adult tumor patient has been described by Close et al.[17]

A middle fossa approach does provide certain advantages. First, there is no need to operate on the middle ear or mastoid, and the patient will not require a closed external ear canal. Second, the facial nerve need not be exposed or rerouted, and possible paresis is avoided. Third, the mandible will not require partial resection or subluxation. Fourth, excellent intracranial exposure is provided, whether the approach is lateral or pterional. (It should be noted that the pterional approach did not permit the same degree of infratemporal fossa exposure as did the preferable lateral middle fossa approach.) Fifth, blood loss in our patients proved minimal. Sixth, both patients had a rapid recovery. Both experienced improved ocular motility and otherwise were active and capable of undergoing chemotherapy and radiotherapy.

COMMENT

Two young patients are described who underwent a middle fossa approach for resection of dumbbell-shape skull base tumors. A definite recommendation for surgery, obviously, cannot be provided by two rare cases. This experience can, however, be added to the cumulative experience in the literature. Surgery was technically possible and well tolerated, and provided excellent exposure with the lateral approach, eliminating the need to operate on the ear, facial nerve, or mandible. In both of these cases, parent and patient satisfaction seemed high.

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SYNDROME OF INAPPROPRIATE SECRETION OF ARGININE VASOPRESSIN IN PATIENTS WITH CANCER OF THE HEAD AND NECK

YOAV P. TALMI, MD
PETAH -TIQVA, ISRAEL

HENRY T. HOFFMAN, MD
IOWA CITY, IOWA

BRIAN F. MCCABE, MD
IOWA CITY, IOWA

The syndrome of inappropriate secretion of arginine vasopressin (AVP) known as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is associated with a variety of malignant and nonmalignant diseases. Only 17 cases of SIADH have been reported in the literature in association with cancer isolated to the head and neck. A retrospective review of 1,436 patients with head and neck malignancy excluding skin cancer through The University of Iowa Tumor Registry revealed 60 patients with the diagnosis of either SIADH or hyposmolality. A chart review for each of these patients was then done to establish the diagnosis of SIADH through relevant laboratory values and by excluding other causes of hyposmolality and hyponatremia. In 43 of these patients (3%), SIADH was found to be associated only with the cancer of the head and neck. We conclude that the incidence of SIADH in patients with cancer of the head and neck is much higher than previously recognized. As elevated serum AVP levels may not be clinically apparent unless associated with excessive water ingestion, it is possible that an even higher percentage of patients may have increased serum AVP levels.

KEY WORDS — cancer, head and neck, SIADH.

INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is associated with a large number of neoplastic and nonneoplastic processes including lung infections, malignancies, and trauma.[1-3] Elevated serum levels of arginine vasopressin (AVP) are not in themselves diagnostic of the clinical syndrome, but indicate the potential for developing SIADH should water loading occur.

Reports of SIADH in association with cancer of the head and neck have been limited to small series totaling 13 cases of squamous cell carcinoma,[4-12] three cases of olfactory neuroblastoma,[12-14] and one case of adenoid cystic carcinoma[15] (Table 1[4-15]). Zohar et al[7] suggested that the incidence of the syndrome in head and neck cancer patients may be higher than previously noted. Symptoms related to the electrolyte abnormalities accompanying SIADH are generally minor and often may be overlooked in patients with the greater morbidity of head and neck cancer. Additionally, in many head and neck cancer patients dehydration may prevent expression of the syndrome.

To establish the incidence of SIADH in a large population of patients with cancer of the head and neck and to further characterize those patients at risk, we performed a retrospective chart survey of patients with head and neck cancer entered over a 10-year period into The University of Iowa Tumor Registry.

METHODS

Patients (1,436) with head and neck malignancies excluding skin cancer and cancer of the thyroid treated at The University of Iowa between 1979 and 1989 were identified through review of the university tumor registry. A computerized review of this data base employing the ICD-9-CM codes for SIADH (253.6) or hyposmolality (276.1) revealed 60 patients for whom one of these two diagnoses had been coded. A detailed chart review for each of these patients was then done to determine the diagnosis of SIADH through a review of relevant laboratory values and by excluding other causes of hyposmolality and hyponatremia. Laboratory values considered compatible with diagnosis of SIADH are low serum sodium, blood urea nitrogen, uric acid, creatinine, and albumin levels, with serum hyposmolality accompanied by inappropriately elevated urine osmolality.[1-4] Patient age, sex, tumor histopathology, and secondary tumors and disease processes, as well as diagnostic and therapeutic procedures, were reviewed for each patient. Thyroid and cardiac disorders were ruled out. Adrenal hypofunction could not be ruled out in all cases. Tumor staging was revised from the clinical description of tumor extent in accordance with the most recent American Joint Committee on Cancer

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From the Department of Otolaryngology–Head and Neck Surgery, The University of Iowa, Iowa City, Iowa. Dr Talmi was a recipient of the American Physicians Fellowship Grant. He is currently affiliated with the Department of Otolaryngology, Hasharon Hospital, Golda Medical Center, Petah-Tiqva, Israel.

REPRINTS — Henry T. Hoffman, MD, Dept of Otolaryngology, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

TABLE 1. PATIENTS WITH SIADH ASSOCIATED WITH CANCER OF THE HEAD AND NECK (LITERATURE REVIEW)

Author	Year	No. of Pts	Tumor Location
Moses et al[4]	1976	2	Larynx
Forrest et al[10]	1978	1	Tongue
Robertson[11]	1978	1	Tongue
Singh et al[12]	1980	1	Nasal neuroblastoma
Srigley et al[14]	1983	1	Olfactory neuroblastoma
Hayes et al[8]	1986	2	Pharynx, oral cavity
Osterman et al[13]	1986	1	Olfactory neuroblastoma
Kandylis et al[9]	1986	1	Pyriform sinus
Okutomi et al[6]	1987	1	Floor of mouth
Abdi and Bishop[5]	1988	1	Tongue
Tatemoto et al[15]	1989	1	Nasal cavity
Zohar et al[7]	1991	4	Larynx (3), pyriform sinus (1)
Total		17	

TABLE 2. ORIGIN AND HISTOLOGY OF PRIMARY TUMOR IN 43 CASES (THE UNIVERSITY OF IOWA)

Anatomic Region	No. of Cases of Squamous Cell Carcinoma*
Oral cavity	24
Hypopharynx	5
Nasopharynx	5 (1)
Larynx	4
Salivary glands	1 (1)
Parapharyngeal space	2

*Numbers in parentheses indicate adenoid cystic carcinoma.

classification.[16]

RESULTS

Ten of 60 patients were excluded from the study because their hyponatremia was transient (under 36 hours) and appeared to result from overhydration in the perioperative period[17] or because insufficient data were available for diagnosing SIADH. The remaining 50 head and neck cancer patients included 34 men and 16 women with ages ranging from 45 to 83 years (mean 64 years, median 62 years). The tumor registry diagnosis included either SIADH (15 patients) or hyposmolality (35 patients). We determined the diagnosis of SIADH in these 50 cases on the basis of reviewing laboratory data, diagnostic test results, and clinical notes. Synchronous lung cancer was seen in 3 patients, and cancer metastatic to the lung in 3 others. An additional patient developed SIADH in the immediate postoperative period that resolved after 5 days. The remaining 43 patients had no identifiable cause for SIADH other than presence of their head and neck malignancy. Advanced tumor stage was present in all 43 patients (stage III 5% and stage IV disease 95%). The site of the primary tumor was the oral cavity in over 50% of the tumors, and all tumors were squamous cell carcinoma except for two adenoid cystic carcinomas (Table 2). Thirty-nine (91%) of the SIADH cases occurred in patients with recurrent tumor.

The status of regional lymph node metastasis during the period of SIADH diagnosis could be established in 28 cases. Thirteen of these 28 patients (46%) had neck disease staged as N3, 3 (11%) had N2 neck disease, and 4 (14%) had N1 neck disease. Eight patients (29%) had no clinically evident lymph node metastasis at the time of diagnosis of SIADH.

Duration of the SIADH could be established in 42 patients and varied from 2 days to over 2 years (mean 2 months, median 28 days). Serum sodium levels ranged from 107 to 133 mEq/L, with a mean of 123 mEq/L. Serum osmolality was found to be recorded in only 4 patients. Only 2 patients had sodium levels below 120 mEq/L, and both suffered from disorientation and lethargy. No correlation between serum sodium level and clinical findings was found in the remainder of the patients. Relevant laboratory data are presented in Table 3.

A total of 11 patients were treated, 8 by fluid restriction and 3 others by adding demeclocycline hydrochloride 600 mg twice a day for an unidentifiable period of time.

DISCUSSION

Although SIADH was initially diagnosed and recorded in only 15 of the 50 cases reviewed retrospectively, clinical and laboratory parameters strongly suggestive of SIADH were present in the other 35. Six of these 50 patients had either primary (3 patients) or metastatic (3 patients) lung disease, and 1 other patient developed postoperative SIADH.

Glucocorticoid deficiency and occasionally complete adrenal cortical insufficiency — Addison's disease — may cause mildly depressed serum sodium concentration with normal potassium and low to normal blood urea nitrogen. Weakness, fatigability, and weight loss are also associated with these disorders.[18] However, other major symptoms of hypoadrenalism, ie, hyperpigmentation, gastrointestinal symptoms, postural hypotension, hypercalcemia, and eosinophilia, were not recorded for the patients in the SIADH group. The overall clinical picture, the transient albeit lengthy course of the hyponatremia, and the clearing of symptoms either spontaneously or

TABLE 3. LABORATORY DATA FOR PATIENTS WITH SIADH AND HEAD AND NECK CANCER (THE UNIVERSITY OF IOWA)

Laboratory Studies	*Normal Values*	*No. of Pts*	*Range*	*Mean*
Serum sodium	135-145 mEq/L	43	107-133	123
Osmolality of urine	350-1050 mOsm/kg	13	346-653	517
Serum	280-300 mOsm/kg	5	196-264	250
Blood urea nitrogen	10-20 mg/dL	43	7-16	10.5
Uric acid	2.4-7.0 mg/dL	40	2.8-6.0	3.6
Creatinine	0.7-1.4 mg/dL	41	0.6-1.4	0.9
Albumin	3.3-5.0 g/dL	38	3.1-5.0	3.8

following definitive treatment all indicate that the underlying disorder was indeed SIADH and not hypoadrenalism. No identifiable cause for inappropriate antidiuretic hormone secretion other than the presence of carcinoma of the head and neck was seen in 43 patients. As a result, this retrospective review identifies a 3% incidence of SIADH among a population of 1,436 patients with head and neck cancer. It should be noted that these patients did not exhibit marked clinical symptoms and in many instances, even in cases lasting for months, SIADH was not identified by the treating physicians. Nineteen of the patients had a duration of SIADH longer than 1 month. Although not necessarily in itself an indication for treatment without clinical manifestations, this form of "chronic" SIADH is not common. At least part of the morbidity suffered by these compromised patients could be attributed to an electrolyte imbalance contributing to the symptoms of fatigue and lethargy. A significant finding of our study is that only 11 of the 43 patients identified with SIADH received treatment.

Odell et al[3,19] characterized the AVP content of blood in patients with carcinoma of the lung and another group with carcinoma of the colon, all without clinical evidence of SIADH. Forty-one percent of the patients with carcinoma of the lung and 43% with carcinoma of the colon had AVP concentrations that were above those in a normal population. Presumably, these patients would manifest SIADH if water intake significantly increased. Several pathophysiologic mechanisms for "inappropriate" secretion of AVP or an AVP-like substance may be considered.

1. Occurrence of SIADH may be related to ectopic secretion of AVP or an AVP-like substance by the tumor.[3,5,15] However, two lines of evidence challenge this view. First, not all tumors studied demonstrated detectable amounts of antidiuretic activity. Second, many patients with cancer and inappropriate antidiuresis have resetting of the osmostat.[20] It is unlikely that malignant tissue would acquire the capacity to both synthesize and osmoregulate AVP, since these functions are normally subserved by different neurons. Indeed, the SIADH was reversed by tumor resection in some cases, but AVP or an AVP-like substance was not detected in the tumoral tissue,[6,13] or its levels were slightly above normal in the serum and negligible in tumoral tissue extract.

2. Secretion of a neurotransmitter or releasing factor for AVP by the tumor is another hypothesis.[11] Hayes et al[8] propose that a substance producing SIADH may be released from malignant cells during the rapid cytolytic phase of tumor destruction by chemotherapy.

3. McQuarrie et al[21] have demonstrated an increased effect of AVP in patients after bilateral simultaneous neck dissection. Pressure on the neck vessels by tumor may also increase cerebral venous pressure, thus inducing release of AVP.

4. Invasion of the vagus nerve (baroreceptor afferents) leading to baroreceptor denervation may lead to hyponatremia.[5,11]

CONCLUSONS

1. The SIADH is encountered in head and neck cancer patients more frequently than formerly reported. A 3% incidence was shown in our series of patients. All patients with SIADH had advanced cancer of the head and neck.

2. Symptoms of fatigue and lethargy in patients with advanced head and neck cancer are easily attributed to their primary disease, whereas they may well be largely consequent to a secondary condition, SIADH. Identification and treatment of that condition can substantially improve their well-being.

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RAT MODEL FOR A VASCULARIZED LARYNGEAL ALLOGRAFT

SCOTT STROME, MD
ANN ARBOR, MICHIGAN

ERIK SLOMAN-MOLL, MD
WASHINGTON, DC

JUSTIN WU
BOSTON, MASSACHUSETTS

BERNADETTE R. SAMONTE
BOSTON, MASSACHUSETTS

MARSHALL STROME, MD
BOSTON, MASSACHUSETTS

A new rat model was developed to reexamine the potential for laryngeal transplantation. The final anatomic derivation evolved from two earlier developmental phases. The first model had only a single arterial anastomosis; the second had an end-to-end arterial anastomosis with an end-to-end arteriovenous shunt. The final product employed an end-to-side arterial shunt and an end-to-side arteriovenous shunt for revascularization. The allografts were sited in tandem with the intact recipient larynges and were not innervated. A total of 16 animals were studied in phase 3; 2 died and the remaining 14 had a 64% arterial patency at intervals of 1 to 14 days. Our purpose is to detail the relevant technical considerations of this new model and compare it with historical controls.

KEY WORDS — allograft, new model, transplantation.

INTRODUCTION

To evaluate the multifaceted field of laryngeal transplantation, we have developed a procedural model using a vascularized laryngeal allograft in the Wistar rat. Advantages relating to cost, graft patency, and recipient survival distinguish this operation from those defined previously. The model, detailed in this paper, can be used to test hypotheses regarding rejection, tissue preservation, and pharmacologic agents.

MATERIALS AND METHODS

The allograft is harvested as follows. An intraperitoneal injection of 1 mL/150 g of chloral hydrate augmented by ether inhalation is used to maintain anesthesia. The skin incision extends from the hyoid bone to the sternal notch. The salivary glands are both removed with a disposable cautery unit. The sternohyoid and thyrohyoid muscles are excised, and the omohyoid muscles are divided to expose the internal carotid arteries. Lateral retraction of the sternocleidomastoid muscles enhances exposure, facilitating use of the dissecting microscope. The common and external carotid arteries are isolated from the vagus nerve, phrenic nerve, and surrounding muscles with jeweler's forceps. The caudal border of the isolation is the sternal notch, and the cephalic portion extends approximately 4 mm above the bifurcation of the superior thyroid artery. The external carotid arteries are ligated and severed above the superior thyroid arteries, with the common and internal carotid arteries left intact. Next, a 0.5-mL intrajugular injection of 100 U of heparinized saline is administered.

The right internal carotid and ascending pharyngeal arteries are isolated microscopically and ligated in tandem, with 7-0 Prolene, 1 mm superior to the carotid bifurcation (see Figure, C). Repetition of the procedure on the opposite side leaves the larynx pedicled on the inferiorly based arterial supply and the pharyngoesphageal enclosure. Following lateral isolation, the lower border of the larynx is freed by transection of the trachea at the second tracheal ring. The cautery is then used for posterior dissection of the larynx from the esophagus. This isolation is continued cephalad to the superior thyroid artery until the larynx is connected to the donor rat only by its vascular pedicle. The carotid arteries are clamped bilaterally at the level of the sternal notch, and the larynx is removed following their transection immediately above the clamps. The donor rat is killed painlessly with an intracardiac injection of chloral hydrate.

The laryngeal graft is immediately immersed in an iced bath of heparinized saline (200 U/10 mL). A 22-gauge intravenous catheter is inserted into one carotid artery, and the graft is flushed with the heparinized saline solution. The end point is the disappearance of

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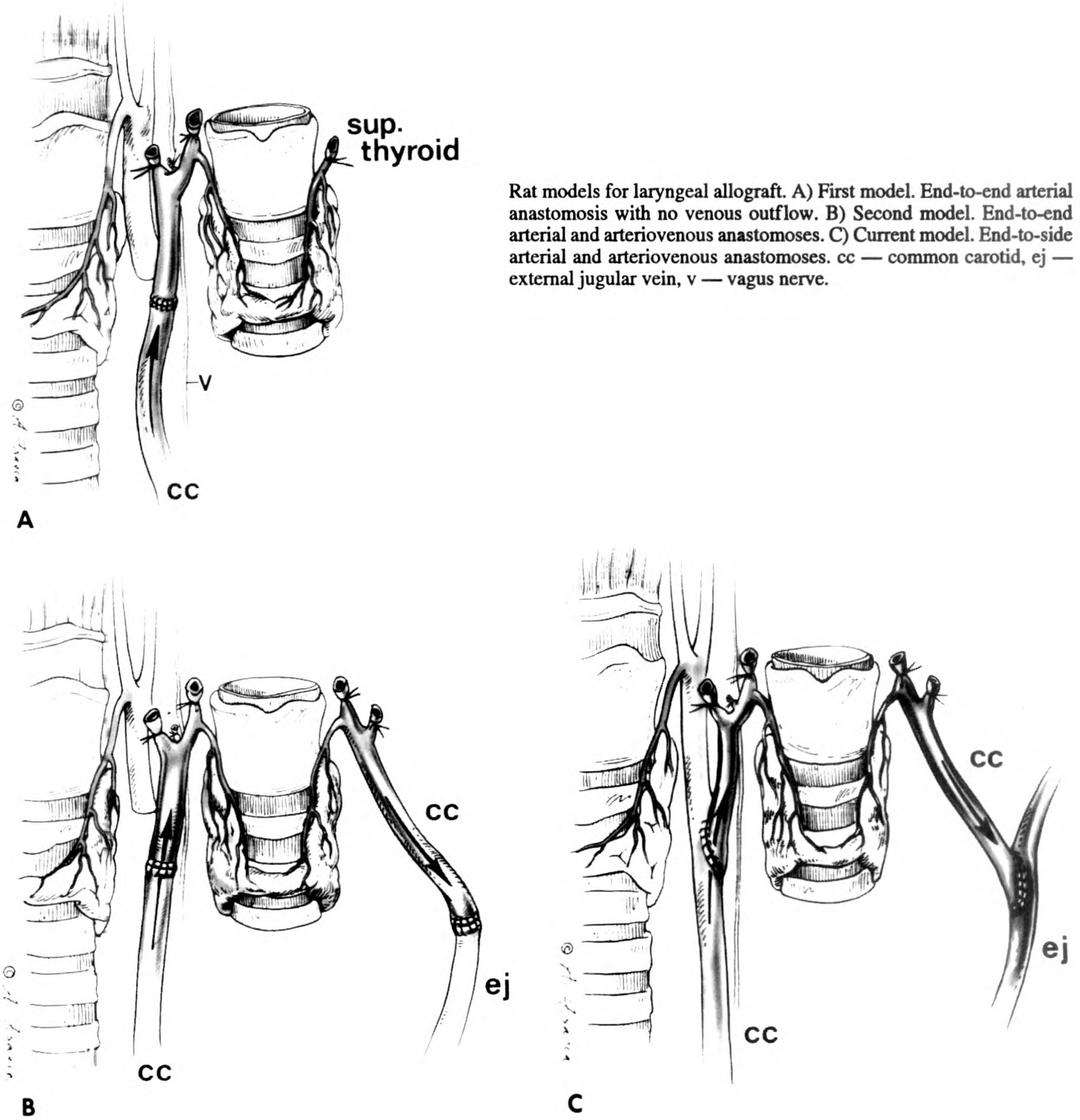
From the Joint Center for Otolaryngology, Brigham and Women's Hospital and Beth Israel Hospital, Surgical Research Laboratories of the Harvard Medical School, Boston, Massachusetts. Supported by the Brigham Surgical Group Foundation, Inc, Brookline, Massachusetts. Dr S. Strome is currently at the Department of Otolaryngology, University of Michigan, Ann Arbor, Michigan. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U. S. C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Harvard Medical School.

REPRINTS — Marshall Strome, MD, 333 Longwood Ave, Boston, MA 02115.



Rat models for laryngeal allograft. A) First model. End-to-end arterial anastomosis with no venous outflow. B) Second model. End-to-end arterial and arteriovenous anastomoses. C) Current model. End-to-side arterial and arteriovenous anastomoses. cc — common carotid, ej — external jugular vein, v — vagus nerve.

the microscopically visible bloody discharge from the opposite carotid artery. It is vital that all blood be removed.

With the graft remaining in solution, a second Wistar rat is anesthetized and prepared in the standard fashion. The incision and removal of the musculature are performed as described for the donor rat, with the dissection being limited to the left side. The carotid artery is exposed and a 1-cm section of the vessel is isolated, approximately 5 mm caudal to the carotid bifurcation. A double microsurgical clamp is attached to the latter segment with a 5-mm gap. With a microscissors, a 2-mm incision is made in the ventral side of the carotid artery, between the clamps. The allograft is removed from the heparinized saline and positioned so that its right internal carotid artery can be anastomosed to the left internal carotid artery of the recipient. An end-to-side anastomosis is performed with 10-0 Prolene. Next, the left internal carotid of the allograft is trimmed to a length at which it can be anastomosed end-to-side to the isolated external jugular vein without kinking or torsion. Removal of the carotid artery clamp is followed by

TABLE 1. PHASE 1 RESULTS

No. of Rats	Survival (d)	Patent AA No.	Patent AA %
1	1	0	0
1	5	0	0
4	7	1	25
Total 6		1	17

AA — arterial anastomosis.

release of the external jugular clamp. Bleeding from the allograft edges is controlled with the cautery, care being taken to avoid the vascular pedicle. A 0.5-mL intrajugular injection of 100 U of heparinized saline is administered, and the wound is closed with a subcuticular stitch. Only one injection of 120,000 U of intramuscular penicillin is administered, and all animals are given oral tetracycline in their water supply.

A skillful microvascular surgeon can complete a full transfer in 3 to 4 hours. The thyroid gland is left on the specimen, as an excellent initial microscopic blood flow within the gland, with an associated return to normal color, is an essential marker of future viability.

RESULTS

Our results are presented in three phases, demonstrating the evolution of the model and the corresponding increase in vascular patency. In phase 1, an end-to-end arterial anastomosis was performed, joining the left common carotid artery of the recipient to the right common carotid artery of the donor. In harvesting the graft, all branches of the right carotid system were ligated, except the superior thyroid artery. The left superior thyroid artery was cauterized as it entered the larynx. In summary, this model employed a single arterial supply to the graft without venous or neuronal anastomoses (see Figure, A).

Six rats were studied. One had a patent arterial anastomosis at 7 days, while the remaining five evidenced thrombosis at the anastomotic sites. All had surrounding hematomas (Table 1). Histologically, rats surviving 1 week had significant granulation tissue around the graft. Despite Boles's study[1] (see Discussion), it seemed apparent that this model would require venous access.

In phase 2, the left superior thyroid artery remained intact, in continuity with the carotid system. The right arterial anastomosis was identical to that used in phase 1, but the donor's left common carotid artery was anastomosed end-to-end with the left external jugular vein of the recipient, providing venous return (see Figure, B). Of the three rats in this series, one died postoperatively of hemorrhage, and the remaining two evidenced thrombus at the arterial anastomosis within 24 hours. Graft edema was qualitatively less than that observed in phase 1. Thrombosis was thought to result in part from a high-flow system being channeled completely into a single small superior thyroid vessel, inducing endothelial injury. In addition, an end-to-end arteriovenous anastomosis resulted in a relative increase in venous backflow pressure, limiting effective venous return. These considerations ended further experimentation with this model. However, both issues were effectively addressed in phase 3.

The surgical procedure for phase 3 is detailed in the Methods section. Sixteen transplants were performed with this protocol, and graft recipients were killed at intervals ranging from 1 to 14 days. Two rats died in the immediate postoperative interval (13% mortality). The remaining 14 rats evidenced an average 64% arterial patency and 43% venous patency (Table 2). All grafts with arterial perfusion were grossly viable, regardless of the status of the venous anastomosis. The viability of this model was confirmed histopathologically.

DISCUSSION

The applicability of this model is best assessed in a historical context. Analyses of prior attempts at laryngeal transplantation are relevant, as they define future areas for investigation. However, the well-known dose-related sensitivity of the dog to xenobiotics has slowed development of several xenobiotics and has not correlated with subsequent human experience. Therefore, the dog, as a model for evaluating new therapeutic modalities, for the most part is passé.

TABLE 2. PHASE 3 RESULTS

No. of Rats	Survival (d)	Ischemic Interval (min)	Patent AA No.	Patent AA %	Patent AV No.	Patent AV %
5	1	58- 88	3	60	2	40
4	3	60- 99	2	50	2	50
3	5	43-100	2	66	2	66
2	14	50- 60	2	100	0	0

Two rats died in postoperative period and are not included in this Table.
AA — arterial anastomosis, AV — venous anastomosis.

The evolution of our animal model in this field has resulted in a product that can serve as a cornerstone for research related to laryngeal transplantation.

Autotransplantation of the canine larynx represented the initial work in this field. In 1966, Boles[1] described a series of operations performed in dogs in which the larynx was either partially or completely resected and then replaced in the same animal. He noted that if the thyroid vessels and nerve supply to the larynx were left intact, the graft would remain viable. Additionally, adequate perfusion could be achieved by using a single craniothyroid artery, never separated from its carotid supply. When the entire laryngeal blood supply was ligated, however, all attempts at reanastomosis failed. This finding suggested that laryngeal viability could be maintained with only limited blood supply when graft innervation remained intact, and that graft failure was secondary to arterial thrombus formation and problems with postoperative management. Our trial with a similar approach in the rat failed, confirming the need for venous return.

In 1967, Takenouchi et al[2] defined four different protocols for vascular reanastomosis of the transplanted canine larynx. In one set of experiments, the craniothyroid arteries were anastomosed primarily, while in the second procedure, these arteries were removed en bloc with the carotid system, and a carotid anastomosis was performed to restore arterial flow. Each of these procedures utilized both single- and double-parameter isolation techniques. Takenouchi et al concluded that graft viability could be maintained via unilateral carotid reanastomosis, and that a 45-minute ischemic interval was the longest that could be tolerated before irreversible anoxic damage occurred to the graft. In a similar study using 11 dogs, Silver et al[3] determined that bilateral carotid reanastomosis was technically feasible and consistent with animal survival. Although these data demonstrated the potential for revascularization of a laryngeal graft, low arterial patency, chronic aspiration, and poor recipient survival prevented widespread acceptance of these models.

The aspiration problem was solved by Silver et al[4] in 1970, with the creation of two stomas. When this advanced model was tested on 18 dogs, 10 survived for longer than 1 week and none developed tracheal occlusion or aspiration pneumonia. Enhanced survival allowed for detailed evaluation of arterial patency. Twenty-one dogs that underwent bilateral carotid reanastomosis and survived for 4 days or longer evidenced only a 29% incidence of graft necrosis. Despite these advances, problems of postoperative management, cost, and the need for large trials initiated our search for an alternative animal species in which laryngeal transplantation could be evaluated. Such studies in humans would not be feasible, as rejection would lead to certain death.

Our goal was to create an animal model for laryngeal transplantation that could be used to test currently undefined parameters relating to graft survival. Initial attempts utilized sheep and dogs, as they afforded the opportunity to compare our data with those from previous experiments. Ultimately, cost, anatomic considerations, and the need for large numbers of animals defined the rat as the most suitable animal consistent with our selection criteria.

In the attempt to restore relatively normal vascular anatomy and decrease the potential for endothelial damage from an abnormal flow state, bilateral end-to-side arterial and venous anastomoses were employed. All viable larynges were submitted for histopathology confirming the viability of the model. Our data compare favorably with those generated from previous canine experiments. Rates of graft necrosis are significantly less than in the majority of historical controls, and postoperative mortality is less than 15%. Low cost, combined with a modicum of required postoperative care, defines this model as suitable for large trials to determine the fundamental criteria for graft life. High rates of recipient survival should subsequently enable us to define the relative applicability of various immunosuppressive drug regimens, and, in particular, their effect on laryngeal tumor growth.

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SOFTWARE REVIEW

THE TMJ SCALE: INCLUDING A COMPUTER PROGRAM DISK AND 74-PAGE ILLUSTRATED MANUAL

Authors: Stephen R. Levitt, Tom F. Lundeen, and Michael W. McKinney.
Company: The Pain Resource Center, Inc, Durham NC; phone (919) 286-4515.
Hardware requirements: IBM-compatible computer; hard disk not required.
Software requirements: The program is fully operational, not requiring an additional data base.
Price: Between $14 and $18 per patient evaluation.

The *TMJ Scale Manual* is a computer program designed to fulfill the need for a self-assessment of temporomandibular joint (TMJ) disorders. In order to create a multidimensional assessment tool for the dentist and physician who attend these ailments, the originators of this program relied on their many years of theoretic and clinical experience with this type of patient. By their own estimate, this program "represents a sophisticated evaluation instrument which has descriptive, discriminative and predictive abilities, and which is based on a self-report symptom inventory."

The computer program is easy to install and run on any standard IBM or IBM-compatible computer, but a basic knowledge of the use of the computer is necessary to expedite its use. A printout is available at the press of a button, but I found setting up a printer to be a little more difficult than the instructions led me to believe.

Patient data are collected in a detailed, descriptive questionnaire given to the patient on the initial visit. The data are easily and quickly entered into the computer, as each question is rated from 1 to 4. The authors tout the questionnaire as a time-saving step because the 97 questions on it are revealing enough to screen for psychosocial and non-TMJ disorders. Because of the nature of TMJ disorders and the personalities with which they are frequently associated, a standardized test hardly seems sufficient. This would seem especially true when it is given impersonally at the initial encounter. These same disadvantages, which are recognized by the authors, exist when trying to standardize diagnostic criteria for any physical disorder.

The program itself is designed to score, record, and print 25 data entries, after which it is exhausted. There is a copy protection on the program that prevents copying or transferring the program to another computer once it has been installed.

The TMJ scale itself is a complex system designed to assess the physical, psychosocial, and global dimensions of the patient's symptoms. The manual goes into exceptional detail about the dimensions, explaining the significance of each. Interestingly, the discussion on the global scale contains five physical symptoms highly predictive of TMJ disorders. Included in the manual are all the statistical data needed for interpretation.

The difficulty with this program is its usefulness as a clinical tool. It adds little to what can be found from a good history and physical examination. The program may speed the process by obtaining the answers to certain basic questions before the patient is seen, however. Those who see only a limited number of TMJ disorders will be less likely to spend the time and money involved in administering this test. The average otolaryngologic practitioner will probably find little use for this particular program in his office.

Two groups that might find the program useful would be practitioners who see a large number of TMJ patients and academic otolaryngologists interested in researching this topic. They would require and benefit from such an efficient method of constant documentation and tracking of TMJ patients. Therein lies the real benefit of using this program: to standardize the symptoms and responses of TMJ patients. The authors should be commended for their scientific approach in the development of this user-friendly program.

CARL M. NECHTMAN, MD
Birmingham, Alabama

Ann Otol Rhinol Laryngol 101:1992

IMAGING CASE STUDY OF THE MONTH

MAGNETIC RESONANCE ANGIOGRAPHY OF SYNCHRONOUS BILATERAL CAROTID BODY PARAGANGLIOMAS AND BILATERAL VAGAL PARAGANGLIOMAS

MAJ MOISES A. ARRIAGA, MC, USAF
LACKLAND AIR FORCE BASE, TEXAS

WILLIAM W. M. LO, MD
LOS ANGELES, CALIFORNIA

DERALD E. BRACKMANN, MD
LOS ANGELES, CALIFORNIA

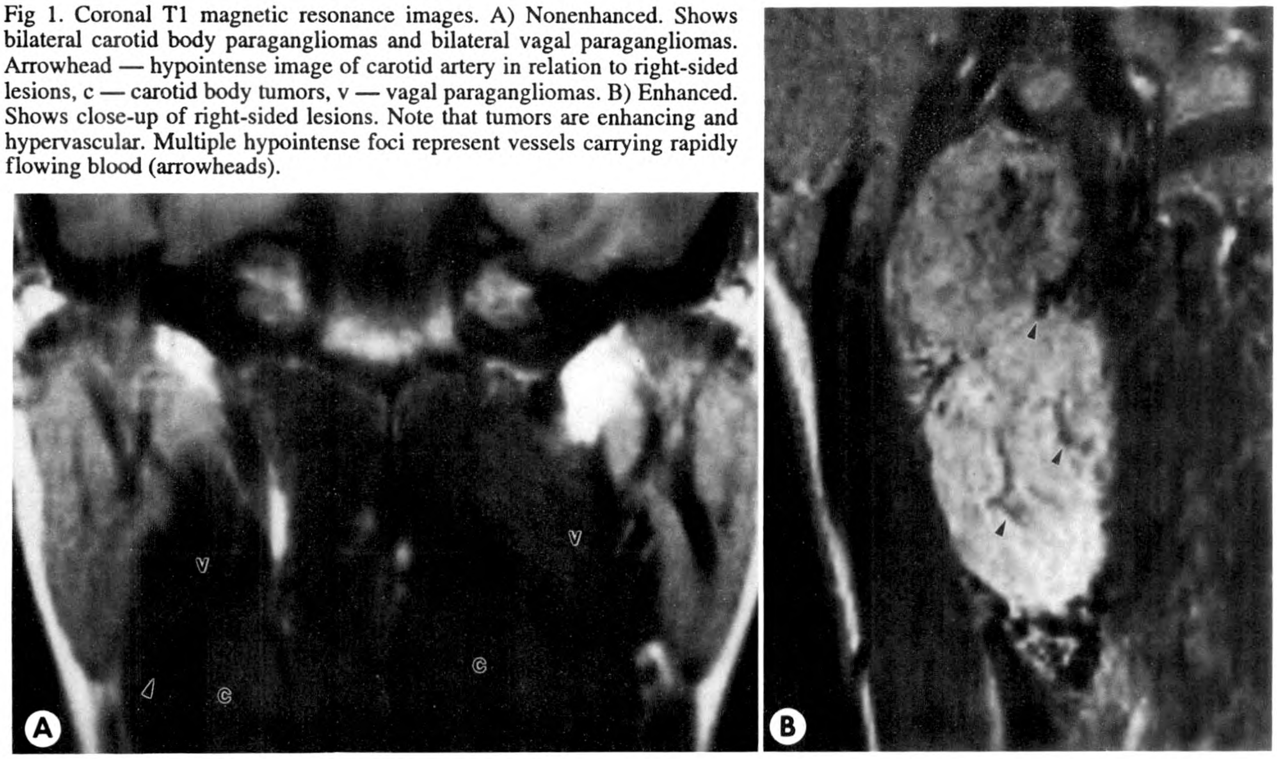
Effective management of head and neck paragangliomas requires close cooperation between the cranial base surgeon and the radiologist in both the diagnosis and treatment of this disease. Carotid and vagal paragangliomas present characteristic clinical and radiographic features that permit a diagnosis without the potential danger of an open biopsy.[1] The magnetic resonance imaging (MRI) features of such tumors have been described. We report the combined use of MRI and a new technique, magnetic resonance angiography (MRA), that permitted the preoperative diagnosis of synchronous bilateral carotid body and bilateral vagal paragangliomas in a patient with bilateral neck masses.

CASE REPORT

A 29-year-old woman was referred for evaluation of bilateral neck masses. She denied neck pain, hoarseness, dysphagia, odynophagia, hemoptysis, hearing loss, tinnitus, or a family history of head and neck tumors.

Physical examination revealed bilateral cervical masses that moved from side to side but not in a

Fig 1. Coronal T1 magnetic resonance images. A) Nonenhanced. Shows bilateral carotid body paragangliomas and bilateral vagal paragangliomas. Arrowhead — hypointense image of carotid artery in relation to right-sided lesions, c — carotid body tumors, v — vagal paragangliomas. B) Enhanced. Shows close-up of right-sided lesions. Note that tumors are enhancing and hypervascular. Multiple hypointense foci represent vessels carrying rapidly flowing blood (arrowheads).



From the House Ear Clinic, University of Southern California School of Medicine (Arriaga, Brackmann), and the Department of Radiology, St Vincent Medical Center (Lo), Los Angeles, California. The opinions expressed are the private views of the authors and do not necessarily represent the views of the Department of Defense or the US Air Force.

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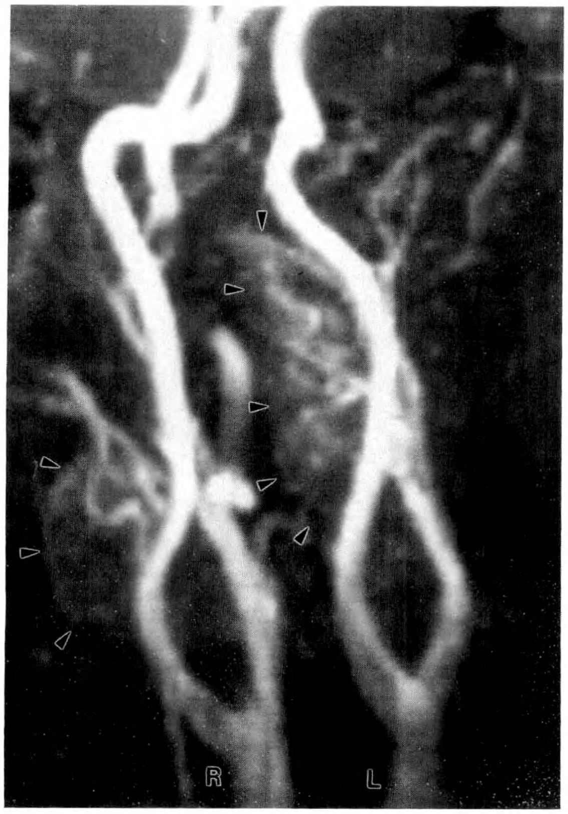

Fig 2. Oblique view of magnetic resonance angiography of bilateral carotid body paragangliomas and bilateral vagal paragangliomas. Arrowheads identify vagal paraganglioma portion of tumor masses. Note that carotid bifurcations are splayed bilaterally by carotid body tumors, and internal carotid artery is deflected anteriorly by vagal paragangliomas. R — right, L — left.

cephalocaudal direction. The left mass was centered at the angle of the mandible and measured 5.5 cm in diameter. The right mass was centered at the level of the hyoid and measured 3.5 cm. Oropharyngeal examination disclosed fullness of the left parapharyngeal space without airway obstruction, and cranial nerves IX, X, XI, and XII functioned normally. The remainder of her neuro-otologic examination findings were normal.

Magnetic resonance imaging with intravenous gadopentetate dimeglumine (Magnevist) demonstrated bilateral, smoothly marginated, ovoid enhancing masses along the internal carotid arteries, with the caudal ends of the masses widening the angle between the internal and external carotid arteries. Multiple fine hypointense foci consistent with vessels carrying rapidly flowing blood were present within the masses (Fig 1). The left-sided mass extended to the superior limit of the poststyloid parapharyngeal space (carotid space). Both masses were bilobed, but the lobes did not appear separable.

Magnetic resonance angiography was performed to demonstrate the relationship of the lesions to the carotid artery and to evaluate the lesions for actual involvement of the carotid artery (Fig 2). There was no narrowing of the lumen of the carotid artery. On both sides the inferior lobes splayed the bifurcation of the internal and external carotid arteries, displacing the former posteriorly — the characteristic "lyre sign" of carotid body tumors. By contrast, the superior lobes on both sides displaced the internal carotid arteries anteriorly — a finding characteristic of glomus vagale tumors.[2] Thus, the diagnosis of synchronous bilateral carotid body paragangliomas and bilateral vagal paragangliomas was based on the MRI findings of bilateral hypervascular masses and the MRA findings of carotid displacements characteristic of carotid body tumors and glomus vagale tumors, respectively.

Conventional intra-arterial contrast angiography confirmed the presence of bilateral hypervascular tumors fed principally from the ascending pharyngeal arteries, but could not clearly separate the carotid body and the vagal components (Fig 3). Embolization was not performed.

The patient underwent removal of a left carotid body paraganglioma and a separate left vagal paraganglioma. Removal of the intravagal lesion necessitated transection of the left vagus nerve. The patient tolerated the procedure well, and has compensated without surgery for the left vagal paralysis. The patient is scheduled for resection of the carotid body tumor on the right. However, resection of glomus vagale lesions usually results in vagal paralysis,[3] and this would result in bilateral vocal cord paralysis for this patient. Thus, the right vagal paraganglioma will be followed radiographically. If the tumor subsequently demonstrates growth, treatment options include embolization, irradiation, or both.

DISCUSSION

Magnetic resonance angiography is a new diagnostic imaging study that exploits the sensitivity of MRI to blood flow.[4] Vessels containing rapidly flowing blood can be isolated from stationary tissues and displayed by themselves without intravascular contrast injection. Three-dimensional information can be viewed in rotation on a monitor and recorded in multiple projections.

Although not yet capable of resolution of smaller vessels visible on selective arteriography, MRA has already found successful application in the detection of stenosis and occlusion of carotid and cerebral arteries, intracranial aneurysms, occlusion of dural sinuses, etc. The imaging characteristics of a carotid body tumor with MRA have been described.[5] This

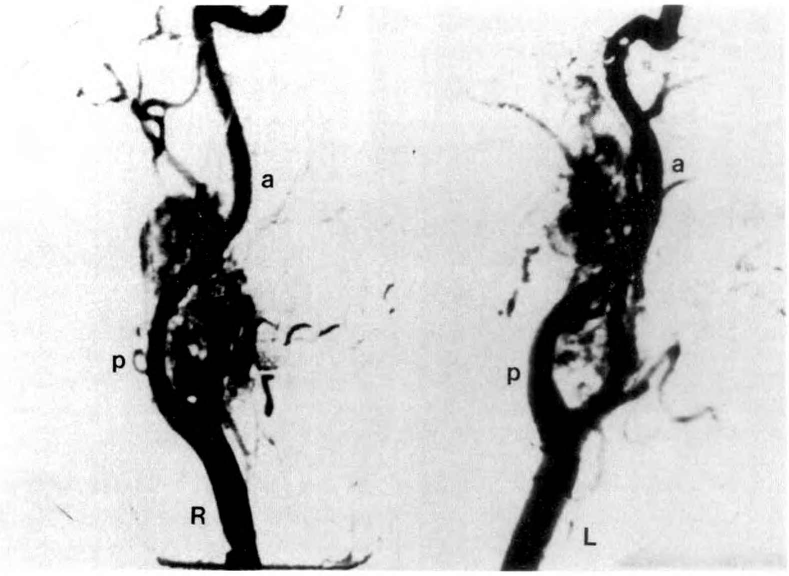

Fig 3. Lateral view of bilateral carotid artery arteriograms of synchronous carotid body and vagal paragangliomas. Carotid body tumors deflect internal carotid artery posteriorly, and vagal paragangliomas deflect internal carotid artery anteriorly. a — anterior, p — posterior, R — right, L — left.

case illustrates the potential role of MRA in multiple paragangliomas.

The role of MRA in paragangliomas depends on the location of the lesion. The value of preoperative embolization of glomus tumors has been recognized.[6] Thus, glomus jugulare patients require conventional angiography for preoperative embolization, and MRA does not offer advantages. However, for carotid paragangliomas, some authorities advise against preoperative embolization.[7] The acute inflammatory response to the embolization particles can obscure the surgical plane between the tumor and the internal carotid artery. If the surgeon prefers not to embolize carotid body and vagal paragangliomas, then MRA offers the advantage of studying the relationship of the tumor to the carotid artery while avoiding invasive carotid artery angiography and its potential morbidity.

CONCLUSION

We conclude that MRA is a useful adjunct in MRI of carotid body and vagal paragangliomas. Where embolization is not required or not feasible, MRA can be an adequate substitute for conventional contrast angiography for demonstration of relationships between masses and vessels.

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Ann Otol Rhinol Laryngol 101:1992

PATHOLOGY CONSULTATION

EMBRYOMA (SIALOBLASTOMA) OF SALIVARY GLANDS

JOHN G. BATSAKIS, MD ROBERT FRANKENTHALER, MD

HOUSTON, TEXAS

There are four clinicopathologic categories of the exclusively major salivary gland tumors that present in the perinatal period. The two with the smallest representation among the 20 cases reported to date are those with a hamartomalike appearance and those with benign adult equivalents — the pleomorphic and monomorphic adenomas. Five cases have been undifferentiated or basaloid salivary carcinomas. Embryomas (sialoblastomas) are the most numerous. These tumors manifest a histologic phenotype like that of the epithelial anlage of the salivary glands, albeit in an arrested state of differentiation.

Fewer than 5% of all salivary gland tumors occur in children.[1] For epithelial neoplasms there is an increasing incidence over the first 20 years. Most are found in children who are between 10 and 20 years of age.[2] The first decade is a relatively spared time, and perinatal (congenital or neonatal) epithelial neoplasms

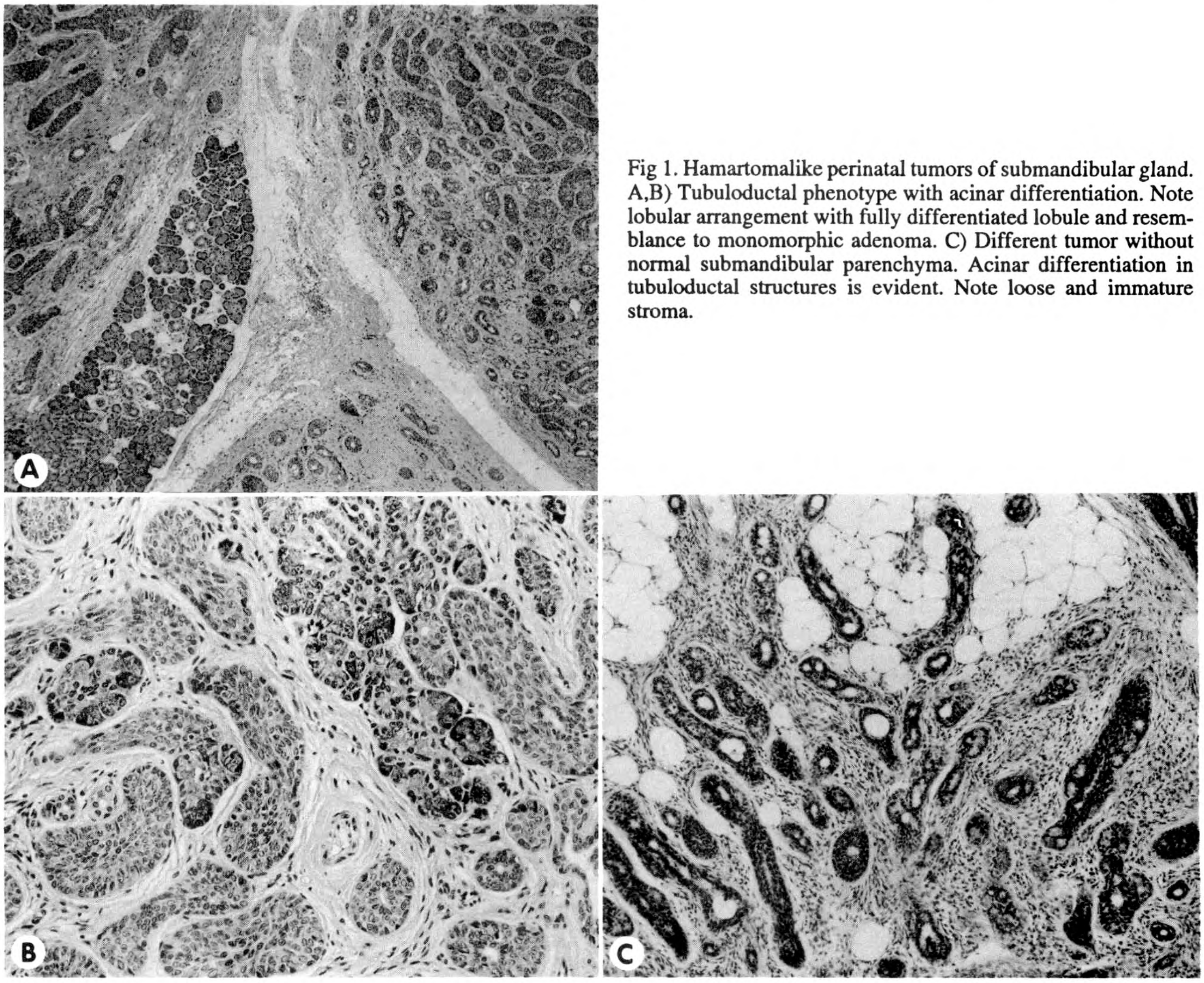

Fig 1. Hamartomalike perinatal tumors of submandibular gland. A,B) Tubuloductal phenotype with acinar differentiation. Note lobular arrangement with fully differentiated lobule and resemblance to monomorphic adenoma. C) Different tumor without normal submandibular parenchyma. Acinar differentiation in tubuloductal structures is evident. Note loose and immature stroma.

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

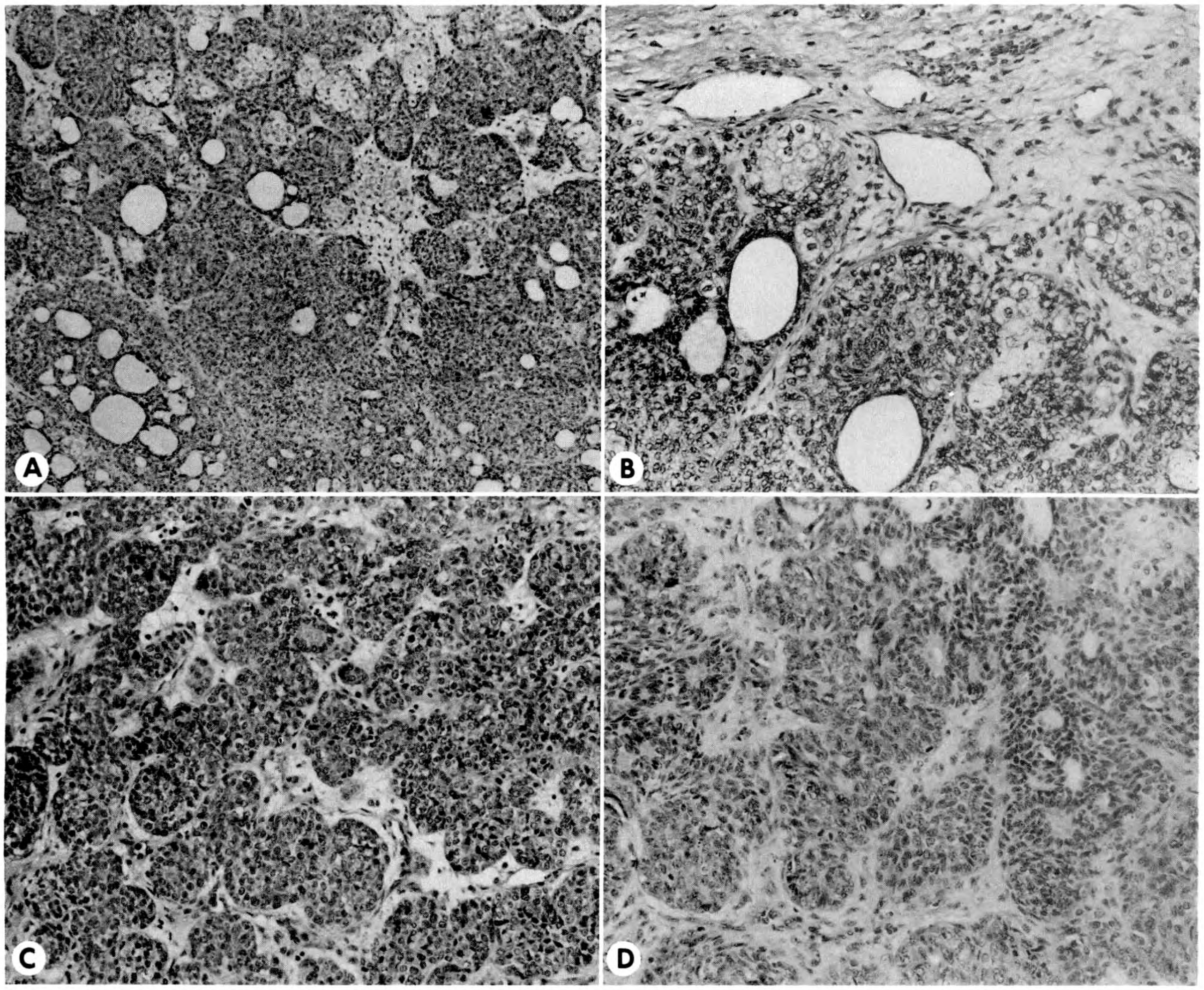

Fig 2. Three parotid gland embryomas that presented in perinatal period. A,B) Solid and embryonic-appearing cell groups. Only demonstrable differentiation features are sebaceous clusters and early ductal space. C,D) Two different embryomas. Both tumors show mitotic figures, not unexpected and not indicating malignancy. C) Minimal differentiation is manifest. D) Attempts at some organization, eg, ducts, are seen.

are in the realm of curiosities.[2,3] As a result, the latter neoplasms pose problems in diagnosis, nomenclature, and management.

Although limitations are imposed by their rarity, differences in terminology, and short follow-up periods, the 20 reported examples of perinatal epithelial salivary gland neoplasms have several distinctive features.[2-5] All have been found in major salivary glands, most prevalently in the parotid gland. Fifteen of the 19 tumors in which the site of origin was identified arose in the parotid gland, the remainder in the submandibular gland. Five of the tumors (25%) were histologically and biologically malignant at the time of their reporting. Three poorly differentiated carcinomas were lethal after distant metastases. Two others, classified as basaloid carcinomas, showed histologic evidence of invasion of nerves, and 1 also had a metastasis to a cervical lymph node. Neither had recurred after surgical removal.

From a histopathologic viewpoint, the perinatal salivary gland tumors fall into four categories: 1) histologically benign with adult counterparts, ie, pleomorphic and monomorphic adenoma; 2) hamartomatous (Fig 1); 3) histologically evocative of the embryonic epithelial anlage of the major salivary glands at various stages of its branching morphogenesis and cytodifferentiation (Fig 2); and 4) histologically and biologically malignant. The adult-type benign tumors are the least common; the anlage-type tumor is the most often encountered.[2]

The histologic appearance of the anlage-type tumors reflects stages during the embryonic development of the major salivary glands. An often mitotically active and primitive cell mass with formative ducts and pseudoductular spaces, without acinar differentiation, recalls the preacinar stages of morphogenesis.[2] A loose, investing mesenchyme with an embryonic appearance completes the embryonic quality of the tumors. The cells (organoblasts), although committed to the development of salivary tissue, remain in a primitive state of organ development and are in a maturation arrest. Either embryoma or sialoblastoma is appropriate as a diagnostic term for this group of congenital salivary gland tumors.[2,3,6]

Hamartomas are further advanced in their morphogenesis and cytogenesis. The embryonic quality of the differentiating cells is no longer evident, and there are acini. Most often the mesenchyme retains a loose embryonic appearance. This type of perinatal tumor seems to have a predilection for the submandibular gland. There is also an indistinct histopathologic border between the hamartomas and some tubuloductal forms of monomorphic adenoma.

Batsakis et al[2] have suggested guidelines for surgical pathologists should they have to deal with these rare tumors: 1) those neoplasms fulfilling criteria for classes of adult salivary gland tumors, eg, pleomorphic adenoma, monomorphic adenoma, undifferentiated carcinoma, or a hamartomatous lesion, should be so designated; 2) neoplasms not able to be classified according to criteria used for adult neoplasms should be called embryoma or sialoblastoma with the additional qualifiers of histologically benign or malignant; and 3) criteria for malignancy in the embryoma-sialoblastoma group should include invasion of nerves or vascular spaces and the ancillary findings of necrosis and a cytologic atypia beyond that expected or presumed for embryonic epithelium. An "invasive" pattern without the foregoing findings is not a reliable feature, since that feature is intrinsic to the salivary gland epithelial primordium.

Until our knowledge of the biologic characteristics of the embryoma-sialoblastoma group of perinatal salivary gland tumor is more advanced, an overly aggressive management beyond surgical removal is not indicated.[2,7]

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20TH INTERNATIONAL CONFERENCE ON COCHLEAR IMPLANTS

The 20th International Conference on Cochlear Implants will be held June 23-25, 1993, at the Ritz-Carlton Hotel, San Francisco, California. For further information, contact University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; (415) 476-4251.

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INDIUM 111–LABELED LEUKOCYTE SCINTIGRAPHY IN EVALUATING HEAD AND NECK INFECTIONS

COMBINED EFFECTS OF NOISE AND CISPLATIN: SHORT- AND LONG-TERM FOLLOW-UP

MAXILLARY SINUS ATELECTASIS

DIAMETER OF THE COCHLEAR NERVE IN DEAF HUMANS: IMPLICATIONS FOR COCHLEAR IMPLANTATION

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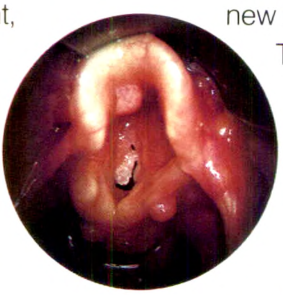

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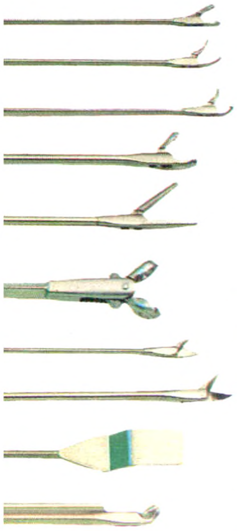

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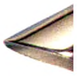

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VOLUME 101 DECEMBER 1992 NUMBER 12

CONTENTS

INDEPENDENT CONTRIBUTIONS

Indium 111–Labeled Leukocyte Scintigraphy in Evaluating Head and Neck Infections
Jeffrey S. Epstein, MD; William I. Ganz, MD; Mark Lizak, MD; Lawrence Grobman, MD; W. Jarrard Goodwin, MD; Mrinal K. Dewanjee, PhD 961

Combined Effects of Noise and Cisplatin: Short- and Long-term Follow-up
Göran F. E. Laurell, MD 969

Maxillary Sinus Atelectasis
Patrick J. Antonelli, MD; Arndt J. Duvall III, MD; Steven L. Teitelbaum, MD 977

Ultrastructural Changes in Human Nasal Cilia Caused by the Common Cold and Recovery of Ciliated Epithelium
Markus Rautiainen, MD; Juhani Nuutinen, MD; Heikki Kiukaanniemi, MD; Yrjö Collan, MD 982

Diameter of the Cochlear Nerve in Deaf Humans: Implications for Cochlear Implantation
Joseph B. Nadol, Jr, MD; Wen-Zhuang Xu, MD 988

Influence of General Anesthesia on Transiently Evoked Otoacoustic Emissions in Humans
Rolf Hauser, MD; Rudolf Probst, MD; Frances P. Harris, PhD; Franz Frei, MD 994

Antibodies Against a 30 Kilodalton Cochlear Protein and Type II and IX Collagens in the Serum of Patients With Inner Ear Diseases
Thomas Joliat, MD; Jerome Seyer, PhD; Joel Bernstein, MD; Marc Krug, PhD; X. J. Ye, MD; J. S. Cho, MD; T. Fujiyoshi, MD; T. J. Yoo, MD, PhD 1000

Spontaneous Remission in Experimental Autoimmune Labyrinthitis
Shigeharu Yamanobe, MD; Jeffrey P. Harris, MD, PhD 1007

SOFTWARE REVIEW

Cochlear Anatomy: A Macintosh Tour
Mitchell K. Schwaber, MD 1015

IMAGING CASE STUDIES OF THE MONTH

Massive Osteolysis (Gorham's Disease) of the Temporomandibular Joint
R. Marvin Freedy, MD; Kenneth A. Bell, MD 1018

Cystic Squamous Cell Carcinoma Metastatic to the Neck From Occult Primary
J. P. Wensel, MD, PhD; J. Michael Talbot, MD 1021

PATHOLOGY CONSULTATION

Nonsquamous Carcinomas of the Larynx
John G. Batsakis, MD; Mario A. Luna, MD; Adel K. El-Naggar, MD, PhD 1024

ANNUAL INDEX

Authors 1029

Subjects 1032

MISCELLANEOUS

Information for Subscribers 12a

Index to Advertisers 14a

Ann Otol Rhinol Laryngol 101:1992

INDIUM 111–LABELED LEUKOCYTE SCINTIGRAPHY IN EVALUATING HEAD AND NECK INFECTIONS

JEFFREY S. EPSTEIN, MD WILLIAM I. GANZ, MD MARK LIZAK, MD
LAWRENCE GROBMAN, MD W. JARRARD GOODWIN, MD MRINAL K. DEWANJEE, PHD
MIAMI, FLORIDA

This retrospective study looked at the role of indium 111–labeled white blood cell (^{111}In WBC) scintigraphy in head and neck infections. The efficacy of ^{111}In WBCs was compared to gallium 67 citrate (^{67}Ga) and technetium Tc 99m methylene diphosphonate (^{99m}Tc MDP) scintigraphy in detecting and monitoring the resolution of infection. For 22 active infections, the sensitivities for ^{111}In WBC, ^{67}Ga, and ^{99m}Tc MDP scintigraphy were 94%, 56%, and 86%, respectively, and the specificities for ^{111}In WBC, ^{67}Ga, and ^{99m}Tc MDP scintigraphy were 100%, 43%, and 0%, respectively. For 8 successfully treated infections, all seven ^{111}In WBC studies became negative after therapy, in as short an interval as 1 month. In contrast, all seven ^{99m}Tc MDP images remained positive for as long as 6 months after therapy. The seven ^{67}Ga studies had variable results, with four (57%) remaining positive, including two (28%) positive at 6 months after therapy. These results suggest that ^{111}In WBC scintigraphy should be the initial radionuclide imaging tool in detecting active head and neck infections because of its greater accuracy, and its ability to revert to normal much sooner than ^{67}Ga or ^{99m}Tc MDP scintigraphs when applied to a subset of patients with resolved infections.

KEY WORDS — indium, osteomyelitis, otitis, radioisotopes, radionuclide studies.

INTRODUCTION

Radionuclide scintigraphy is valuable in the diagnostic evaluation of head and neck infections.[1,2] Technetium Tc 99m methylene diphosphonate (^{99m}Tc MDP) and gallium 67 citrate (^{67}Ga) are the radiotracers most often used. Both agents accumulate in normal bone, in sites of osteomyelitis, and in a variety of noninfectious osseous processes including fractures and neoplasms.[1-5] The ^{99m}Tc MDP and ^{67}Ga isotopes also localize in pathologic soft tissue sites.

Unbound indium 111 (^{111}In) chloride preferentially binds to transferrin, and only a small fraction binds to circulating cellular elements.[6] To optimize detection of infection, ^{111}In is bound to a patient's leukocytes obtained from autologous donor blood. The ^{111}In-labeled white blood cells (^{111}In WBCs) accumulate in sites of acute and chronic infection, in sites of nonspecific inflammation, and rarely in neoplasms such as lymphoma.[2,7,8] For detecting acute infections, ^{111}In WBC scintigraphy has a reported sensitivity of 80% to 95%, and a specificity of greater than 95%, making it more accurate than other isotopes in diagnosing infection.[4,8-11]

The high specificity and sensitivity of ^{111}In WBC imaging should make it effective for monitoring response to antibiotic therapy. Scintigraphy with ^{67}Ga has been shown in the literature to better reflect clinical resolution than ^{99m}Tc MDP imaging in patients undergoing successful antibiotic therapy for malignant external otitis,[12,13] osteomyelitis of the base of skull,[14] and other clinical syndromes,[2,3] and is suggested to be useful in the evaluation of anti-infective therapy.[15] Several clinical reports have found ^{111}In WBC imaging also to be accurate in demonstrating infection resolution.[16] There is just one report on a head and neck infection, a case of malignant external otitis, in which ^{111}In WBC imaging results became normal after anti-infective therapy.[17]

There is a scarcity of published data regarding the clinical utility of ^{111}In WBC scintigraphy in diagnosing head and neck infections.[2,9] The purpose of this retrospective study is to compare the efficacy of ^{111}In WBC to ^{67}Ga and ^{99m}Tc MDP scintigraphy in detecting infections and in monitoring the clinical response of anti-infective therapy.

MATERIALS AND METHODS

SCINTIGRAPHIC TECHNIQUE

Technetium Tc 99m Methylene Diphosphonate Bone Scanning. A dose averaging 20 mCi (740 MBq) of ^{99m}Tc MDP is injected. Three hours later, moving camera imaging of the whole body or bone scintiphotos (using on each view the time required to obtain 700,000 counts over the anterior chest) is performed with a general all-purpose collimator. Single photon emission computed tomography (SPECT) images of the head are obtained with a 20% window centered at 140 keV on a general all-purpose collimator for

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From the Departments of Otolaryngology–Head and Neck Surgery (Epstein, Lizak, Grobman, Goodwin) and Nuclear Medicine (Ganz, Dewanjee), University of Miami and Jackson Memorial Hospital, Miami, Florida.

REPRINTS — Jeffrey S. Epstein, MD, Dept of Otolaryngology (D-48), PO Box 016960, Miami, FL 33101.

TABLE 1. SENSITIVITY OF THREE RADIOISOTOPES IN DETECTION OF ACUTE INFECTIONS

	^{111}In WBCs			^{67}Ga			^{99m}Tc MDP		
Disease	*Pos*	*Neg*	*Sens (%)*	*Pos*	*Neg*	*Sens (%)*	*Pos*	*Neg*	*Sens (%)*
Sinusitis	4	1	80	1	2	33	3	0	100
Otologic	3	0	100	5	1	83	6	0	100
Osteo of BOS	1	0	100	5	0	100	5	0	100
Mastoiditis	2	0	100	0	1	0	1	0	100
Dental	5	0	100	1	2	33	2	0	100
Neck abscess	1	0	100	0	1	0	0	0	0
Adenopathy	2	0	100	1	1	50	0	2	0
Osteo of maxilla	1	0	100	1	0	100	1	0	100
Total	16	1	94	9	7	56	12	2	86

WBCs — white blood cells, MDP — methylene diphosphonate, Pos — positive, Neg — negative, Sens — sensitivity, Osteo — osteomyelitis, BOS — base of skull.

superior topographic resolution in cases of otologic infections. The SPECT images are acquired by using 64 steps over 360° at 40 seconds per view. The SPECT study is reconstructed with a 0.5 cycles per pixel frequency and an order of five Butterworth filter on a 64 x 64 x 16 pixel unit matrix after attenuation correction using the Chang method.[18]

Gallium 67 Citrate Scanning. A mean dose of 5 mCi of ^{67}Ga is injected. By using a general all-purpose collimator, moving table imaging of the whole body or region of interest scintiphotos (using in each view the time required to obtain 400,000 counts over the anterior chest) is performed with two or three photopeaks with a 20% window 3 to 5 days after injection. When an earlier diagnosis is required, 3- to 6-hour postinjection images are obtained. When indicated, SPECT images are obtained (by using the same protocol as the bone SPECT).

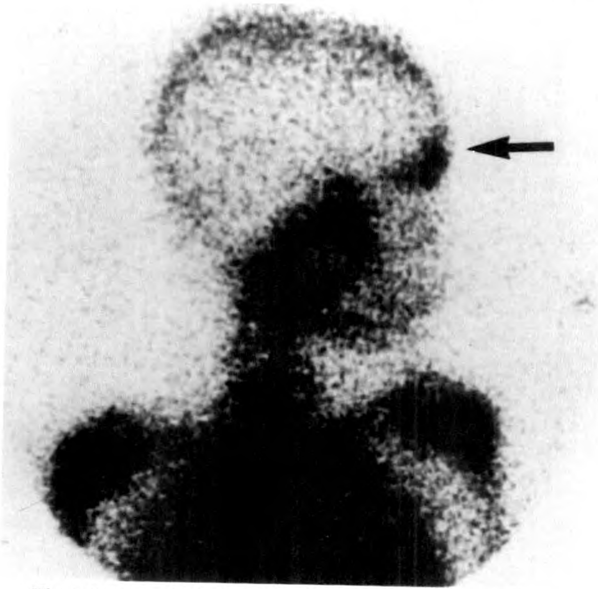

Fig 1. Image of 16-year-old girl with Crohn's granulomatous colitis. In workup for chronic headaches, hypogastric pain, and fever, total body ^{111}In WBC scintigraphy displayed increased uptake in frontal sinus region. Paranasal sinus computed tomogram was consistent with frontal sinusitis. Pictured is right lateral view of head with increased ^{111}In WBC uptake in frontal sinus (arrow).

Indium 111 White Blood Cell Scanning. The preparation technique of the labeled leukocyte suspension has previously been validated[6]; under sterile conditions, 100 mL of venous blood is collected, anticoagulated, and allowed to sediment by using Hetastarch. After removal of plasma, the resultant supernatant containing cellular elements is sequentially centrifuged at 600 and 800 rpm to remove red blood cells and platelets, respectively. The WBC button is incubated with 250 to 500 μCi of indium-oxine for 30 minutes to obtain a labeling efficiency greater than 90%. Five milliliters of plasma are added to the ^{111}In WBCs, then 200 to 500 mCi of viable ^{111}In WBCs are reinjected into the patient's venous blood within 4 hours. Planar 15-minute images are obtained 4 and 24 hours later.

SCAN INTERPRETATION

Interpretation of the scans was performed by three readers. The initial reading was nonblinded because of the need for accurate clinical diagnosis. Subsequent readings were blinded. Readers used strict criteria for a positive scan as demonstrating greater activity than a contralateral site or adjacent bone, with computer quantitation as needed to eliminate interpreter bias on equivocal cases. Transaxial two-pixel computer quantitation was obtained from profiles on the coronal image showing the most abnormal radiotracer uptake. When the symptomatic to asymptomatic side demonstrated more than a 20% increase in counts, this was used to confirm abnormal radioactive uptake. Readers used early (3- to 6-hour) ^{67}Ga and ^{111}In WBC images to confirm findings on delayed images and to detect infections earlier.

PATIENT ANALYSIS

A retrospective review was conducted of 17 patients with a variety of head and neck infections. Subjects came from one of three University of Miami affiliated hospitals. The 9 female and 8 male patients ranged in age from 16 to 75 years old. Fifteen patients

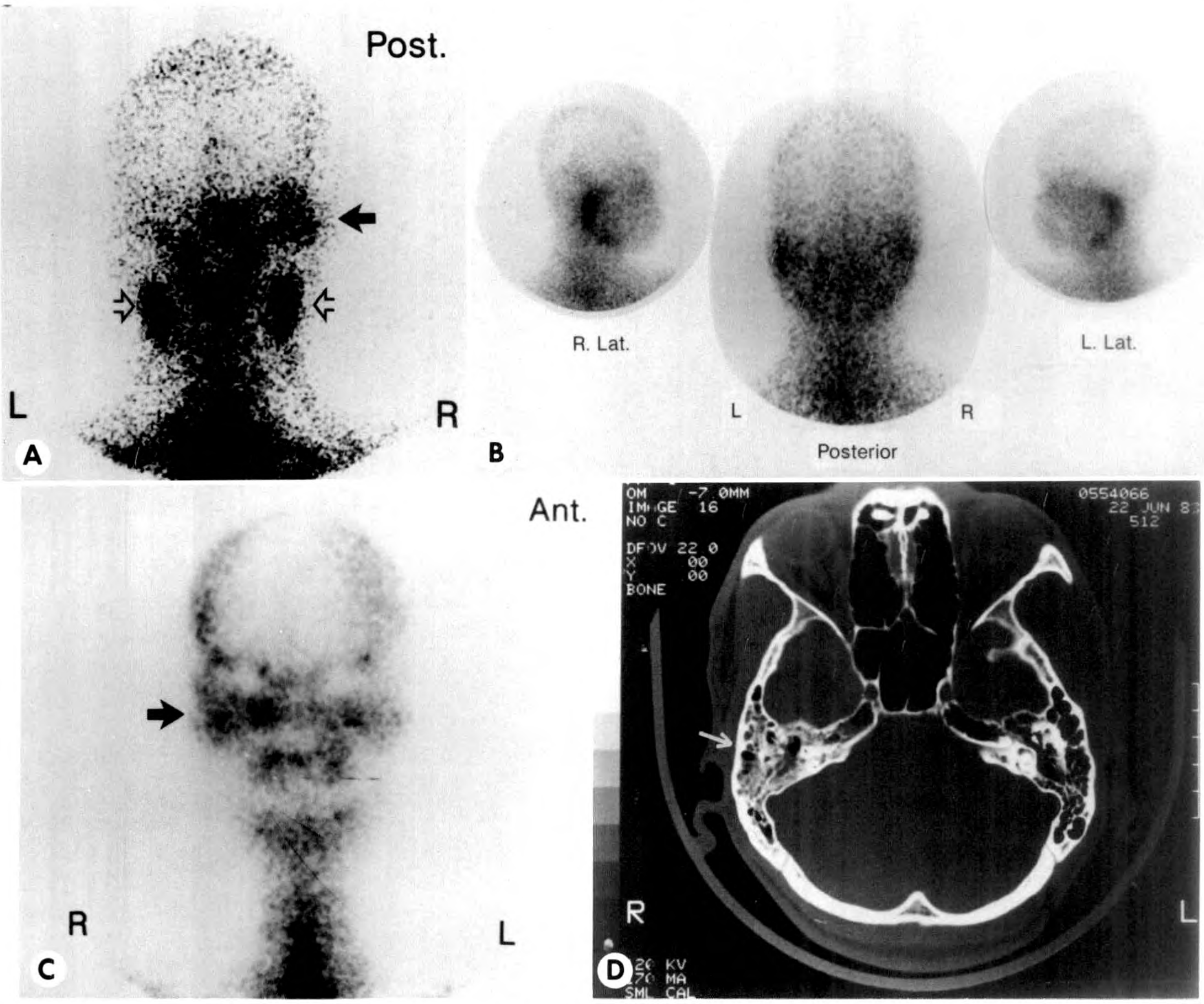

Fig 2. Images of 26-year-old man, human immunodeficiency virus–positive, insulin-dependent diabetic, who presented with otalgia of right ear and bilateral tender jugulodigastric adenopathy. A) Scintigraphy with ^{111}In WBCs, in posterior view, reveals increased uptake in region of right temporal bone and mastoid (solid arrow) and intense activity of bilateral jugulodigastric nodes in neck (open arrows). B) Scintigraphy with ^{67}Ga, in posterior and lateral views, reveals symmetric uptake in bilateral mastoid regions, negative for focal process. C) Bone scintigraphy with ^{99m}Tc MDP, in anterior view, reveals mildly elevated activity in right temporal bone region (arrow). D) Axial computed tomogram reveals well-aerated left epitympanum and mastoid bone, and opacified right epitympanum and mastoid air cells (arrow). Conclusion is that in this case, scintigraphy with ^{111}In WBCs and ^{99m}Tc MDP was superior to that with ^{67}Ga for diagnosis of mastoiditis. For diagnosis of cervical adenopathy, ^{111}In WBC scintigraphy was superior.

presented to the nuclear medicine department with a diagnosis of a specific head and neck infection, and 2 patients presented with an unknown site of infection. Five patients had more than 1 infection, for a total of 22 infections. The majority of patients had two or more radionuclide imaging studies, with the scintigraphic protocol individualized for each patient. A total of 13 ^{111}In WBC scans, 10 ^{67}Ga scans, and 11 ^{99m}Tc MDP scans were obtained. All but 4 subjects had at least one correlative computed tomography (CT) or magnetic resonance imaging (MRI) scan. All areas of positive uptake were verified by clinical follow-up and/or by pathologic specimens.

Also included in this study were 8 patients with successfully treated head and neck infections, 4 of whom were included in the first group of 17 subjects with active infections. Radionuclide scintigraphs were obtained at various intervals following the completion of anti-infective therapy. The interval between the clinical resolution of disease (considered to occur when antibiotic therapy was discontinued) and the performance of the scintigraph determined the duration of disease-free time before specific results appeared as normal.

Four ^{111}In WBC scintigraphs performed on patients with infections at non–head and neck sites were also included, serving as noninfections for specificity calculations. Because an excess of radionuclide is

TABLE 2. RESOLVED INFECTION BY DIAGNOSIS AND RESULTS OF NUCLEAR SCINTIGRAPHY

		^{111}In WBCs		^{67}Ga		^{99m}Tc MDP	
Disease	*No.*	*Pos*	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*
Total	8	0	6	4	3	7	0
Mastoiditis	2	0	2	1	0	2	0
MEO	1	0	1	1	0	1	0
Osteo of BOS	4	0	2	1	3	4	0
Dental	1	0	1	1	0		

Number refers to number of infections; not all patients were imaged with all three radioisotopes.

MEO — malignant external otitis; for other abbreviations, see Table 1.

administered, uptake in the head and neck was felt not to be affected by uptake at a distant site.

STATISTICAL ANALYSIS

Separate analysis was carried out for both active and resolved infections. For active infections, the sensitivity of a scan was defined as the number of true-positive studies divided by the total number with documented infection. Specificity was defined as the number of true-negative studies divided by the total number without infection (resolved infections and, for ^{111}In WBC, we used the four patients with non-head and neck infections). Cochran Q test with χ^2 analysis was performed on the subset of patients on whom the three different types of nuclear scans were obtained ($k = 3, f = 2$).

RESULTS

Among the 22 active head and neck infections, the two most common sites were the paranasal sinuses (6) and the mastoid or base of skull (7). Six of the infections were osteomyelitis: 5 of the mastoid or base of skull, and 1 of the maxilla. Two patients had reactive cervical lymphadenopathy, five had dental infections, and one had a neck abscess.

The radionuclide scintigraphs obtained on the 22 infections included ^{111}In WBCs (N = 17), ^{67}Ga (N = 16), and ^{99m}Tc MDP (N = 14; Table 1). The sensitivity of ^{111}In WBC, ^{67}Ga, and ^{99m}Tc MDP scintigraphy was 94%, 56%, and 86%, respectively. Cochran Q test statistical analysis was limited to seven patients scanned with all three isotopes and did not show statistical difference ($p > .05$).

Figures 1 and 2 illustrate the images obtained by radionuclide scintigraphs and conventional radiographs in two head and neck infections, demonstrating the superior sensitivity of ^{111}In WBC.

The radionuclide scintigraphs obtained on the eight patients with successfully treated infections included ^{111}In WBCs (N = 6), ^{67}Ga (N = 7), and ^{99m}Tc MDP (N = 7). The results of images by diagnosis are summarized in Table 2. Seven of the eight infections were otologic in origin: four were osteomyelitis of the base of skull, two were otomastoiditis, and one was malignant external otitis. There was one odontogenic periapical abscess. Osteomyelitis of the skull base was a complication of malignant external otitis in all four cases. Both cases of mastoiditis were complicated by intracranial extension of infection. All seven patients with otologic disease were aggressively treated with intravenous antibiotics, and follow-up radionuclide scintigraphs were obtained at various intervals following therapy. The odontogenic infection was treated with surgery and antibiotics.

The results of radionuclide scintigraphy by the duration of time from infection resolution are summarized in Table 3. In two cases, imaging was performed within 1 month of the resolution, in three cases the interval was from 2 to 5 months, and in the remaining three, there was a 6-month or greater interval. For the eight successfully treated infections, all six ^{111}In WBC studies became negative after therapy, in as short an interval as 1 month. In contrast, all seven ^{99m}Tc MDP images remained positive, for as long as 6 months after therapy. The seven ^{67}Ga studies had variable results, with four (57%) remain-

TABLE 3. RESOLVED INFECTION BY INTERVAL BETWEEN RESOLUTION AND RESULTS OF NUCLEAR SCINTIGRAPHY

		^{111}In WBCs		^{67}Ga		^{99m}Tc MDP	
Interval (mo)	*No.*	*Pos*	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*
1	2	0	2	2	0	2	0
2-3	2	0	1	0	1	1	0
4-5	1			0	1	1	0
6	3	0	3	2	1	3	0

Number refers to number of infections; not all patients were imaged with all three radioisotopes.

For abbreviations, see Table 1.

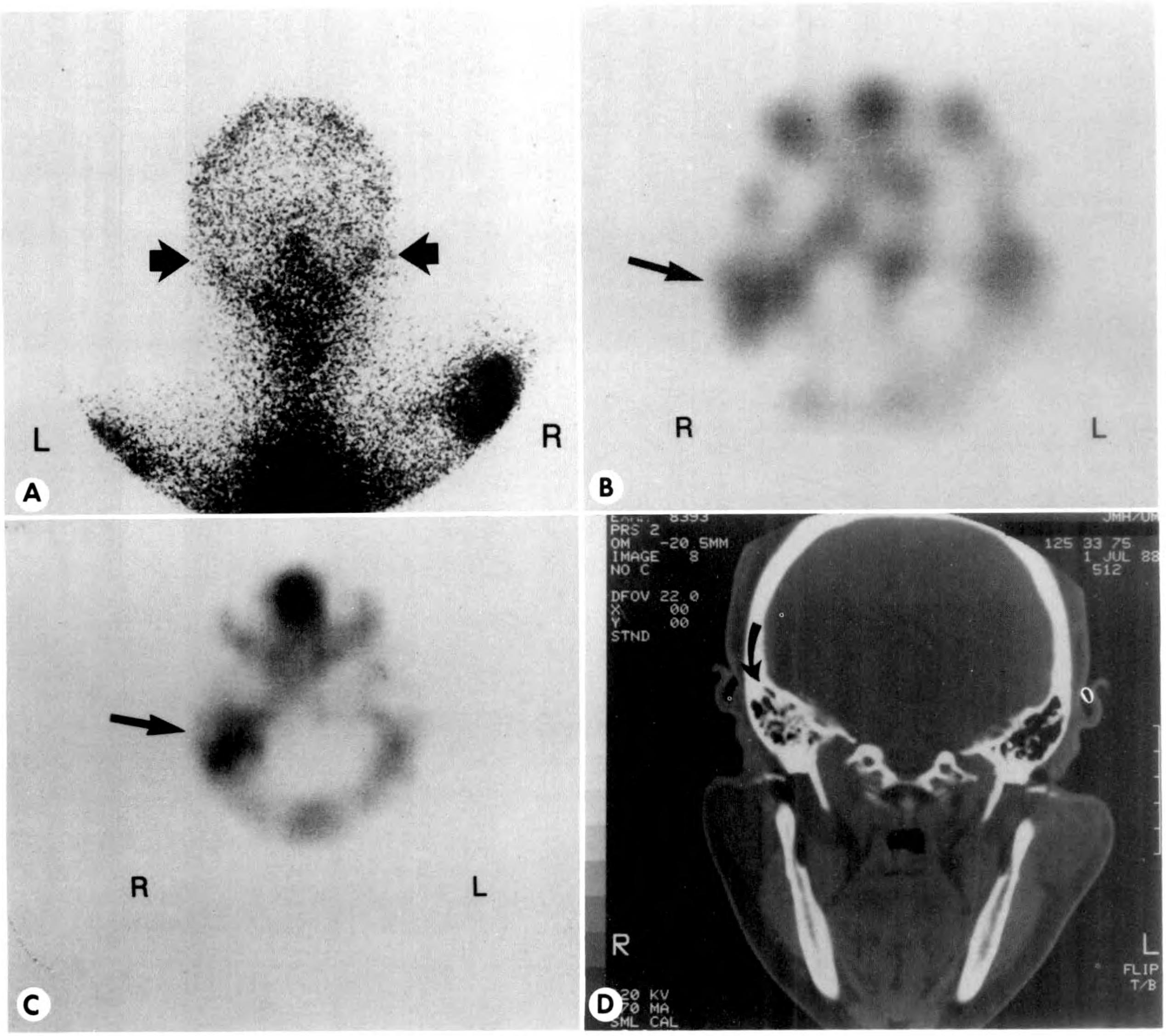

Fig 3. Images of 62-year-old woman, insulin-dependent diabetic, treated with intravenous antibiotics for malignant external otitis in right ear. Nuclear scanning was performed 4 weeks after therapy. A) WBC scintigraphy with ^{111}In WBCs, in posterior view for best visualization of temporal bones and base of skull, reveals symmetric uptake in bilateral mastoids (arrows) consistent with resolved infection. B) Single photon emission computed tomography (SPECT) scintigraphy with ^{67}Ga provides improved topographic resolution. This axial cut reveals moderately increased right mastoid activity (arrow) consistent with persisent disease. C) SPECT scintigraphy with ^{99m}Tc MDP shows strong signal in right mastoid region (arrow) on axial view consistent with positive scan. D) Coronal computed tomogram, performed after 2 weeks of therapy, reveals opacified right mastoid and no bone destruction (arrow), consistent with resolving mastoiditis. In summary, at 1 month after clinically successful therapy, only ^{111}In WBC scintigraph has reverted to normal.

ing positive, including two (28%) positive at 6 months after therapy. Figures 3 and 4 illustrate the images obtained with radionuclide scintigraphs and conventional radiographs in two resolved infections. The SPECT imaging with ^{67}Ga and ^{99m}Tc MDP radioisotopes was superior in site localization. High-resolution CT or MRI provided assistance in localization of infection.

The specificity for ^{111}In WBC imaging was 100%, calculated from the four non–head and neck infections and the six resolved infections. The specificity for ^{67}Ga and ^{99m}Tc MDP imaging, calculated from the seven resolved infections, was 43% and 0%, respectively.

DISCUSSION

The results of ^{111}In WBC scintigraphy were better than those of ^{67}Ga and ^{99m}Tc MDP scintigraphy in the diagnosis of 22 various head and neck infections. The 94% sensitivity and 100% specificity of ^{111}In WBC imaging are consistent with previous reports.[8,9,11,19] The low (56%) sensitivity of ^{67}Ga scintigraphy is due to false negatives with sinus, dental, and neck disease. The high false-negative rate for ^{67}Ga imaging in

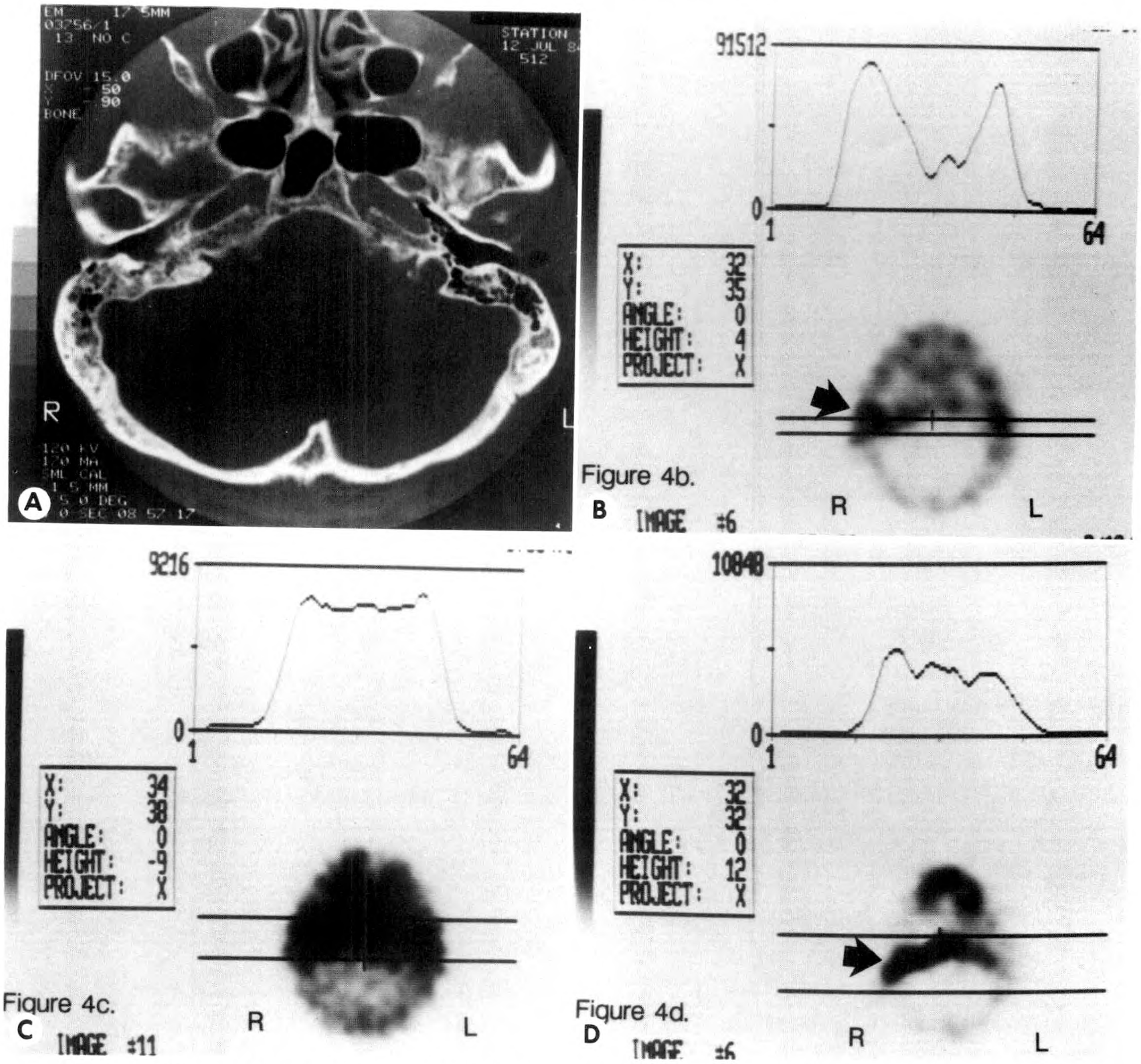

Fig 4. Images of 75-year-old man, insulin-dependent diabetic, who developed osteomyelitis of base of skull as complication of malignant external otitis in right ear. Computed tomography scan at presentation and serial ^{67}Ga scintigraphs provide visualization of response to successful antibiotic and hyperbaric oxygen therapy. A) Axial computed tomogram reveals sclerotic right mastoid and ill-defined bone posterior to external auditory canal consistent with osteomyelitis. B) SPECT imaging with ^{67}Ga performed at presentation. Quantitative uptake reveals asymmetric right mastoid activity (arrow). C) SPECT quantitative imaging with ^{67}Ga after 5 months of therapy reveals resolution of disease. D) SPECT quantitative image with ^{99m}Tc MDP is still positive (arrow) after 5 months of therapy. In summary, ^{67}Ga image became negative 3 to 5 months after disease resolution, while at 5 months there was residual ^{99m}Tc MDP activity.

sinusitis is consistent with a previous planar imaging study involving Asian patients in which ^{67}Ga uptake was greater in cases of carcinoma than in chronic sinusitis.[20] Fineman et al[11] report radionuclide imaging with ^{111}In WBC to be superior to imaging with ^{67}Ga in sinusitis in patients both with and without acquired immunodeficiency syndrome. The low active bone marrow content of the paranasal sinuses and mastoid region, associated with improved ^{111}In WBC imaging, is a reasonable explanation for its imaging superiority to ^{67}Ga in these regions.[21] In addition, normal nasopharyngeal ^{67}Ga uptake may obscure detection of pathologic paranasal ^{67}Ga accumulation. The high sensitivity and low specificity of ^{99m}Tc MDP in infections are similar to those in previous studies.[3,4,8]

Scintigraphy with ^{111}In WBCs can be effectively performed on patients with alterations in the hematopoietic system. In two other clinical series, ^{111}In WBC imaging has shown good results in immunosuppressed transplant patients and patients seropositive for human immunodeficiency virus.[2,11] In our series, both the one patient with acquired immunodeficiency syndrome and the one on immunosuppression to prevent donor transplant kidney rejection had good results with ^{111}In WBC imaging. There is a paucity of objective data in the literature as to the effect of steroids on ^{111}In WBC scintigraphy, presumably secondary to inhibition of leukocyte chemotaxis.[9] The effect of antibiotics on scintigraph sensitivity is probably inconsequential.[9,22] Leukopenia is not a contraindication for ^{111}In WBC scintigraphy, as compatible donor WBCs can be used.[6]

Radionuclide scintigraphy is effective in detecting osteomyelitis of the base of the skull and its precursor disease, malignant external otitis.[1,12,14] In the detection of chronic osteomyelitis, some studies in the literature have found ^{111}In WBC scintigraphy very effective, with a greater than 85% sensitivity.[16,19] However, other investigators have demonstrated a lower sensitivity of ^{111}In WBC for detecting chronic osteomyelitis.[4,8] The ^{67}Ga and ^{99m}Tc MDP isotopes, because they accumulate at sites of bone remodeling regardless of cause, have a low specificity for chronic osteomyelitis, especially in sites of previous surgical intervention.[3,8] This is a situation not uncommon in patients with otologic, paranasal sinus, and other head and neck infections. While the interpretation of ^{67}Ga imaging studies can be aided by the comparison of simultaneous ^{99m}Tc MDP imaging studies, ^{67}Ga scintigraphy has been found to be a reliable indicator of infection in only 25% to 33% of patients with existing bone disease.[4,23] In this study, ^{111}In WBC scintigraphs accurately diagnosed osteomyelitis of the skull base and malignant external otitis.

Regarding the accuracy of ^{111}In WBC scintigraphic detection of chronic soft tissue infections, there is discrepancy in the literature. Some investigators have observed equal sensitivity for ^{111}In WBC scintigraphy for both acute and chronic infections,[19] while others have found that only in active infections characterized by an acute inflammatory response is there a reliable accumulation of the isotope.[4,7,24] This discrepancy is possibly related to WBC preparation techniques, as suggested by Merkel et al.[25] Viable preparations of the ^{111}In WBC isotope are important for good results. The only false-negative ^{111}In WBC study in our investigation was in a case of an infected fat-obliterated osteoplastic flap surgical site. This infection seems to have behaved like an abscess, with limited ^{111}In WBC infiltration.

In successfully treated infections, ^{111}In WBC scintigraphs reverted to negative in the shortest duration of time. The ^{67}Ga scintigraphs inconsistently reverted to normal in approximately 3 to 6 months. The ^{99m}Tc MDP, by accumulating in healing bone sites, produced positive images for as long as 6 months after therapy. While based on a small number of patients, the time duration for scintigraph conversion to negative was as short as 1 month for ^{111}In WBC, 2 to 3 months for ^{67}Ga, and greater than 6 months for ^{99m}Tc MDP imaging.

The advantage of radionuclide scintigraphy over conventional radiographic imaging techniques is the ability to detect functional and physiologic alterations that occur before structural changes are visualized by CT scans and plain x-ray studies.[2,8,13] For skull base imaging, nuclear magnetic resonance imaging is inferior, since the only marrow-containing bone, necessary for imaging, is the clivus.

Because of low radioactivity, the ^{111}In WBC isotope has limited use in conventional SPECT imaging, such as in the detection of brain abscesses.[26] Both ^{67}Ga and ^{99m}Tc MDP provide better SPECT information density. The triple-headed SPECT instruments, newly available at our institution, provide improved SPECT ^{111}In WBC images and reduce imaging time. A new radiotracer under investigation at our institution is ^{99m}Tc WBCs. Several reports have found this isotope to be a rapid and reliable detector of abdominal infectious processes.[27] In addition, the high photon flux of the ^{99m}Tc WBC isotope permits improved WBC SPECT imaging. We are presently obtaining SPECT images with ^{99m}Tc WBCs that we think are preferable to low-count ^{111}In WBC SPECT studies. We are not aware of any reports to date on the use of ^{99m}Tc WBC scintigraphy in the imaging of head and neck infections.

CONCLUSION

We propose an algorithm for the sequential imaging of head and neck infections using the different mechanisms of isotope uptake. First performed is planar and, if possible, SPECT ^{99m}Tc MDP scintigraphy, a nonspecific but sensitive and inexpensive screen for infection. A negative ^{99m}Tc MDP image is followed by a repeat study after several weeks of observation. A positive ^{99m}Tc MDP study is followed by ^{111}In WBC scintigraphy, a specific and sensitive study for both acute and chronic infections. If available, triple-headed detector SPECT ^{111}In WBC imaging can provide improved tomographic resolution; SPECT imaging with ^{99m}Tc WBC or ^{67}Ga isotopes is an alternative. Because labeled WBC scintigraphs may miss infections if the isotope is not viable or if leukotaxis is limited, ^{67}Ga imaging may have a role in chronic infections. Scintigraphy with ^{67}Ga should not be performed within 1 week prior to ^{111}In WBC imaging because of the long half-life of ^{67}Ga, which can interfere with subsequent ^{111}In WBC scintiphotos; at 1 week, 23% of the ^{67}Ga citrate isotope has not decayed.[28] Radioimaging with ^{67}Ga can be performed immediately following imaging with ^{111}In WBCs because of the low injected dose of ^{111}In WBC isotope and the higher photopeaks used with ^{67}Ga.[28] Because of the need to evaluate the role of SPECT ^{99m}Tc-labeled WBCs, further studies are ongoing. Because of the 6-hour half-life of ^{99m}Tc and the higher photopeaks of ^{67}Ga,[28] we are evaluating the use of SPECT ^{99m}Tc-labeled WBCs prior to using SPECT ^{67}Ga.

For monitoring the response to anti-infective therapy, our results suggest that radioimaging with ^{111}In WBCs is better than that with ^{67}Ga or ^{99m}Tc MDP. A negative ^{111}In WBC study provides a high level of confidence that the infection has resolved.

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COMBINED EFFECTS OF NOISE AND CISPLATIN: SHORT- AND LONG-TERM FOLLOW-UP

GÖRAN F. E. LAURELL, MD

STOCKHOLM, SWEDEN

The combined effects of noise exposure and intravenous cisplatin injection on electrophysiologic hearing thresholds in guinea pigs were studied with short-term and long-term follow-up. The combined effects on the permanent threshold shift were dependent on the order of exposure. A potentiation was achieved when noise exposure preceded cisplatin injection by 30 minutes or by 3 days. Cisplatin injection 2 or 3 days before noise exposure produced no significant potentiation or inhibition. The combined effects on the temporary threshold shift were not influenced by the sequence of exposure.

KEY WORDS — permanent threshold shift, potentiation, temporary threshold shift.

INTRODUCTION

The chemotherapeutic drug cisplatin has been tested against a number of solid tumors, but it has been most useful in the treatment of testicular cancer.[1] The ototoxicity of cisplatin is one side effect that is rarely seen with other anticancer drugs. Two ototoxic symptoms may occur after cisplatin treatment: tinnitus and hearing loss.

The risk of ototoxic side effects in patients undergoing cisplatin therapy is influenced by several defined and unknown factors. The best-studied variables that contribute to hearing loss are the amount of the single dose[2-5] and the cumulative dose.[3-6] There is a considerable variation in susceptibility to cisplatin-induced hearing loss that can be only partially explained by the peak plasma concentration after drug administration.[5] The relationship between pretreatment hearing loss and cisplatin-induced ototoxic symptoms is controversial, since contradictory results have emerged. A finding of clinical importance is that a prior sensorineural hearing loss does not increase the risk of further impairment during cisplatin therapy.[4-7] Sensorineural hearing loss is composed of several pathologic entities with different etiologic factors, eg, aging, noise, and genetic predisposition. Noise damage is of particular significance, since noise is the only factor that can be readily influenced. Studies on the combined effects of noise and cisplatin thus have an experimental interest.

An ototraumatic interaction between cisplatin and noise,[8,9] as well as a pharmacodynamic interaction between cisplatin and other ototoxic drugs like loop diuretics[10-13] and aminoglycoside antibiotics,[14] has been reported. The mechanism of interaction is likely to be dependent on the respective structural and functional injuries in the cochlea. The combined impact of noise exposure and cisplatin administration might in certain situations even be seen as a potentiation (excessive response to the two factors, producing more than an additive effect).

There is a clear difference between the cytotoxic action of cisplatin on cochlear structures on the one hand and that on vestibular structures on the other hand, since no vestibular neuroepithelial damage has been found.[15,16] It has been demonstrated in several animal studies that administration of cisplatin results in damage to the outer hair cells (OHCs) of the organ of Corti; this is most pronounced in the basal turn.[17-19] The damage to the OHCs in both the basal and the second turns is dependent on the dose given.[16] The morphologic site of noise-induced injury in the cochlea depends on the frequency characteristics of the noise, the sound level, and the time of exposure. Both inner hair cells (IHCs) and OHCs are susceptible to noise.[20,21] A complex pattern of ototraumatic interaction between cisplatin and noise may therefore be expected.

The aim of the present study was to examine the combined effects of broadband noise exposure and a single intravenous (IV) injection of cisplatin on electrophysiologic hearing thresholds in guinea pigs. The specific questions investigated were as follows.

1. Is there a potentiation between noise exposure and cisplatin administration?
2. Are the sequence and the time interval of exposure of importance for the combined effects?
3. Do the combined effects yield different results for temporary threshold shift (TTS) and permanent threshold shift (PTS)?

From the Department of Physiology, Karolinska Institute, Stockholm, Sweden. Supported by Tysta Skolan and the Swedish Work and Environment Fund.

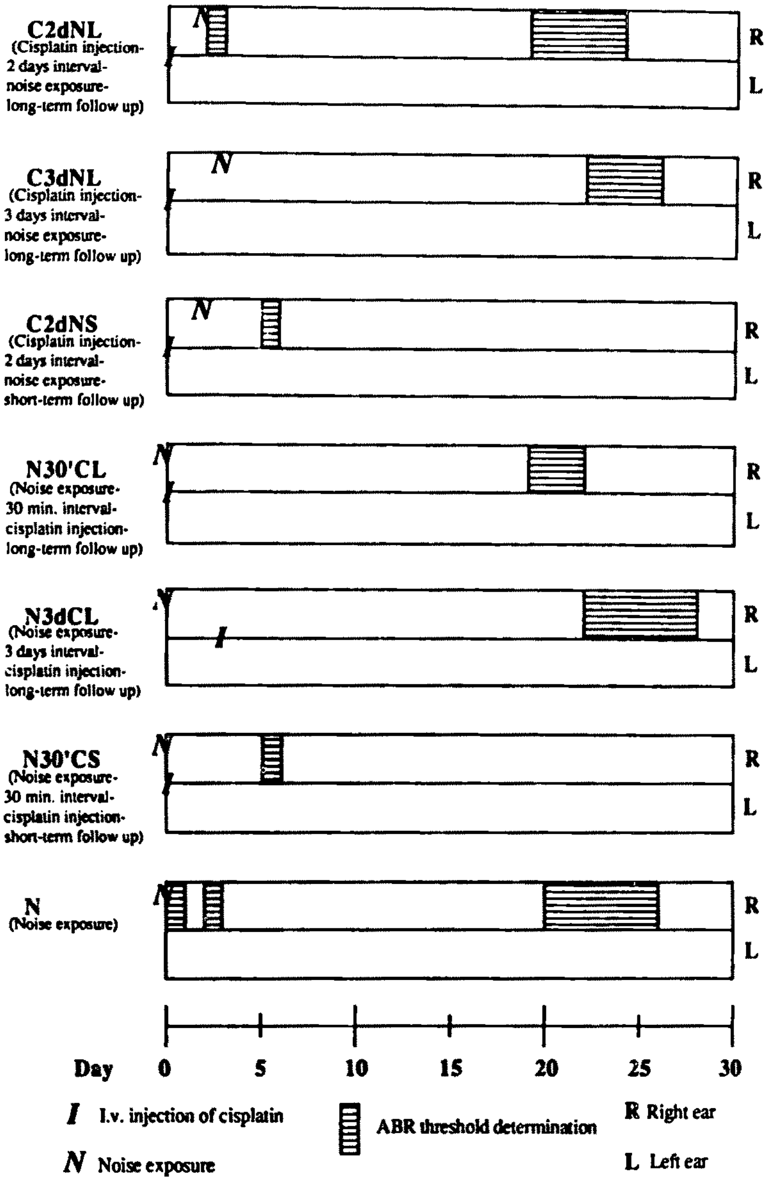
C2dNL
(Cisplatin injection-2 days interval-noise exposure-long-term follow up)
C3dNL
(Cisplatin injection-3 days interval-noise exposure-long-term follow up)
C2dNS
(Cisplatin injection-2 days interval-noise exposure-short-term follow up)
N30'CL
(Noise exposure-30 min. interval-cisplatin injection-long-term follow up)
N3dCL
(Noise exposure-3 days interval-cisplatin injection-long-term follow up)
N30'CS
(Noise exposure-30 min. interval-cisplatin injection-short-term follow up)
N
(Noise exposure)
R
L
Day
0
5
10
15
20
25
30
I I.v. injection of cisplatin
N Noise exposure
ABR threshold determination
R Right ear
L Left ear

Fig 1. Schedule of cisplatin administration, noise exposure, and auditory brain stem response determination for seven groups of guinea pigs.

MATERIAL AND METHODS

The experiments were performed on 79 pigmented guinea pigs of both sexes (230 to 540 g). No sign of external ear or middle ear infection was found before the treatment. All animals had electrophysiologic hearing thresholds in the normal range prior to noise exposure and cisplatin injection. The animals were divided into seven groups to study the influence of different intervals and temporal orders for the combined effects of cisplatin administration and noise exposure. Figure 1 shows the treatment schedule for the different groups.

NOISE EXPOSURE

The animals were anesthetized and placed on a heated table to prevent body shivering that could disturb the noise exposure. All animals were unilaterally exposed for 30 minutes to a broadband noise, 1.5 to 5 kHz, of 137 dB sound pressure level (SPL). Noise was generated by a 1381 random noise generator (General Radio Company) in conjunction with a filter and an amplifier and delivered in a closed system with a hearing aid telephone (Oticon Power) as the driving source. The earphone was attached to the ear by a plastic tube inserted in the ear canal. The spectrum of the stimuli and the SPL were monitored before and after sound overstimulation by a 3528 A spectrum analyzer (Hewlett Packard) and a 2610 measuring amplifier in the linear setting (Brüel & Kjaer), respectively. The measurements were made by connecting the noise-producing earphone to a 1/4-in Brüel & Kjaer microphone in a plastic chamber at a distance of 15 mm.

CISPLATIN ADMINISTRATION

The anesthetized animal was placed on its back

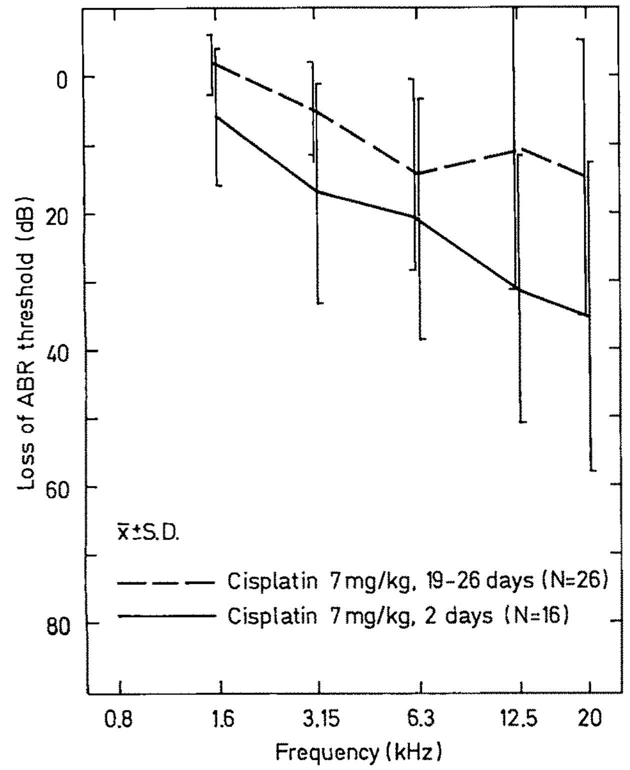

Fig 2. Effect of single intravenous injection of cisplatin at 7 mg/kg body weight. Shows mean auditory brain stem response (ABR) threshold loss 2 days and 19 to 26 days after injection.

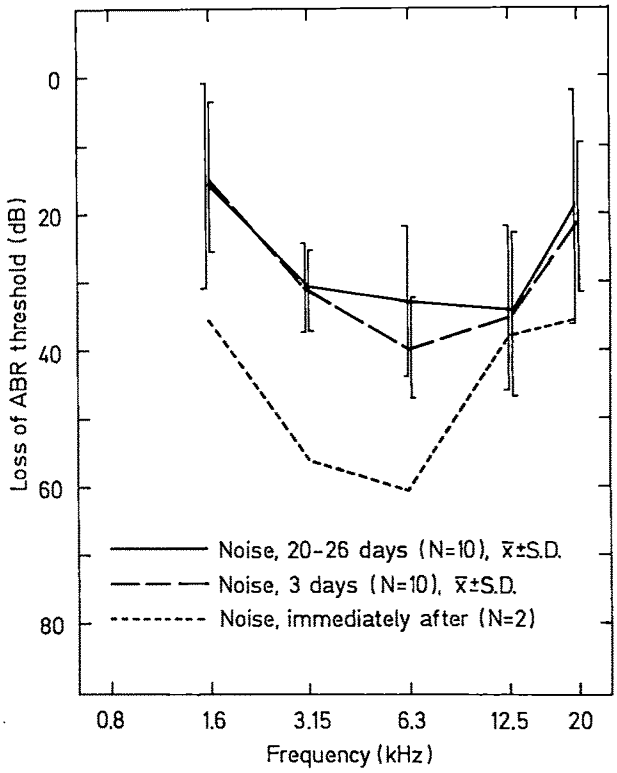

Fig 3. Effect of broadband noise exposure for 30 minutes. Shows mean ABR threshold loss 3 and 20 to 26 days after exposure.

and the external jugular vein was exposed. Cisplatin was injected as a bolus into this vein at a concentration of 0.5 mg/mL in an isotonic solution.

BRAIN STEM AUDIOMETRY

Thresholds of the auditory brain stem response (ABR) were obtained from anesthetized animals. The thresholds were established separately for both ears in all animals. The stimuli were single full-cycle sine waves, filtered with a 1/3 band-pass filter (Brüel & Kjaer, type 1617) centered at the frequency of the sine wave.[22] The stimuli were presented at a rate of 20/s from a TDH 39 earphone connected to the ear with a 10-cm tube (outside diameter 8 mm) coated with acoustic absorbant material to prevent resonance. The electrical signals were picked up by subcutaneous needle electrodes between the vertex and the ipsilateral retroauricular region, with a reference electrode placed on the back. The electrical activity was amplified 10^4 times, band-pass-filtered between 50 and 4,700 Hz, and fed into a Datalab 4000 signal averager. The ABR was based on the average of 2,000 epochs. The thresholds were determined for five frequencies: 1.6, 3.15, 6.3, 12.5, and 20 kHz. The thresholds of the ears of 11 healthy guinea pigs served as normal material and were used as a reference for calculations of the hearing loss.[8] In cases in which the ABR threshold could not be reached, the hearing threshold was set to approximately 5 dB over the limit of the equipment (roughly 75 dB above the normal guinea pig ABR threshold).

FIRST SERIES

In the first series we studied cisplatin injection before noise exposure.

Long-term Follow-up. "Group C2dNL" (cisplatin injection — 2-day interval — noise exposure — long-term follow-up) consisted of 18 guinea pigs, 9 surviving. Each animal was given an IV cisplatin injection of 7 mg/kg body weight. Two days later they were unilaterally exposed to noise, ie, 1 to 2 days before the ototoxic effect of cisplatin reaches a maximum.[23,24] This dose of cisplatin was chosen because it is between 5 mg/kg (no effects on electrophysiologic hearing thresholds obtained with frequency-specific ABR) and 8 mg/kg (substantial ABR threshold shift).[24] The ABR thresholds were determined 2 and 19 to 24 days after cisplatin injection. The second threshold determination was used to study the effect on PTS.

"Group C3dNL" (cisplatin injection — 3-day interval — noise exposure — long-term follow-up) consisted of seven guinea pigs, six surviving. The animals received an IV injection of 7 mg/kg body weight, and were unilaterally exposed to noise 3 days later. The ABR thresholds were determined 23 to 26 days after cisplatin injection.

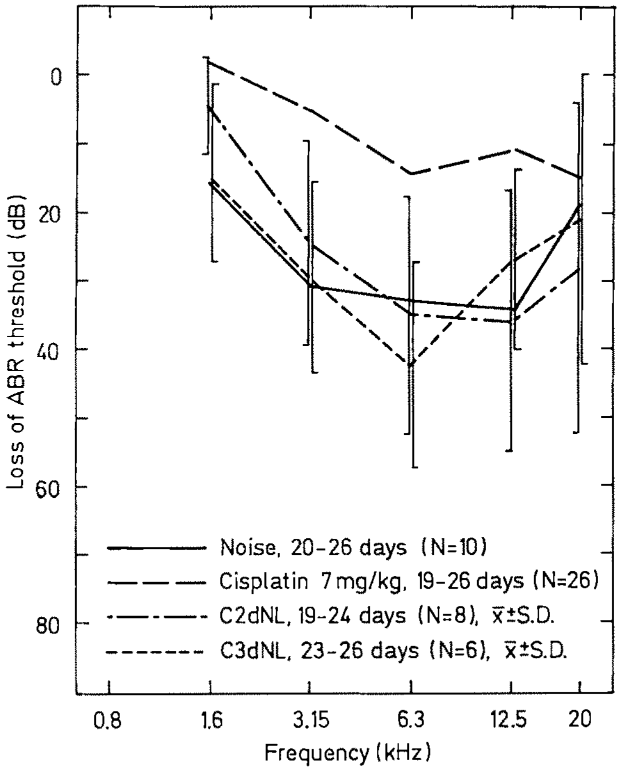

Fig 4. Mean loss of ABR thresholds in guinea pigs receiving cisplatin injection before noise exposure. Reference audiograms for cisplatin-induced and noise-induced threshold shifts, respectively, are also included.

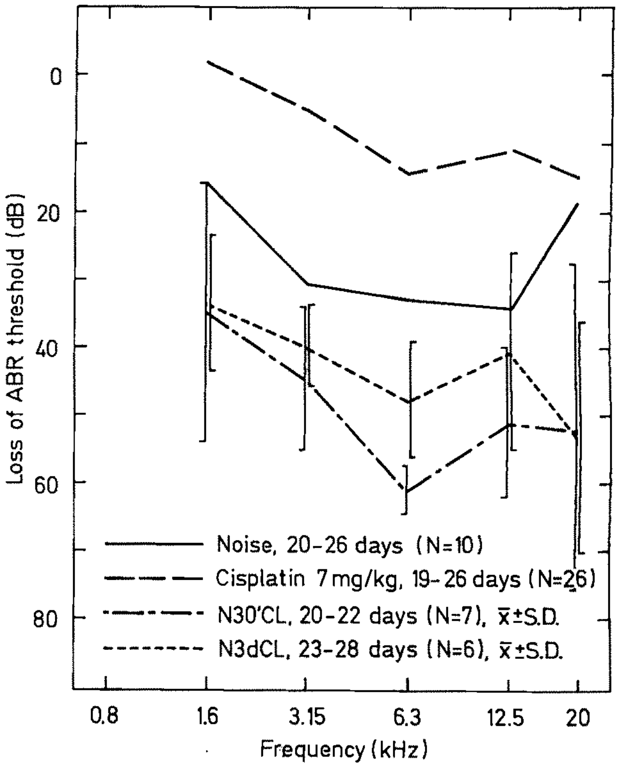

Fig 5. Mean loss of ABR thresholds in guinea pigs undergoing noise exposure before cisplatin injection. Reference audiograms for cisplatin and noise-induced threshold shifts, respectively, are also included.

Short-term Follow-up. "Group C2dNS" (cisplatin injection — 2-day interval — noise exposure — short-term follow-up) consisted of seven guinea pigs, six surviving. This group was used to study the acute combined effects of a cisplatin injection and noise exposure without any long period of recovery before the final measurement. Each animal was given an IV dose of 8 mg/kg, which is close to the LD50 dose (9.7 mg/kg by a single intraperitoneal injection, according to Fleischman et al[17]). The right ear was exposed to noise 2 days later. The ABR thresholds were determined 5 days after cisplatin injection.

SECOND SERIES

The second series studied noise exposure before cisplatin injection.

Long-term Follow-up. Group N30'CL (noise exposure — 30-minute interval — cisplatin injection — long-term follow-up) consisted of 18 guinea pigs, 7 surviving. The reversed combined effects were studied at the time of greatest TTS after noise exposure. The animals were unilaterally exposed to noise and 30 minutes later were given an IV cisplatin injection of 7 mg/kg body weight. The ABR thresholds were determined 20 to 22 days after the noise exposure.

Group N3dCL (noise exposure — 3-day interval — cisplatin injection — long-term follow-up) consisted of eight guinea pigs, six surviving. In this group the combined ototraumatic effects were studied with a longer interval between noise exposure and cisplatin injection. The animals were unilaterally exposed to noise. After 3 days, when the temporary component of the noise-induced threshold shift had recovered, they received an IV cisplatin injection of 7 mg/kg body weight. The ABR thresholds were determined 3 and 23 to 28 days after noise exposure.

Short-term Follow-up. Group N30'CS (noise exposure — 30-minute interval — cisplatin injection — short-term follow-up) consisted of seven guinea pigs, five surviving. As with group C2dNS, the combined effects with a short interval were studied in this group. The right ear of each animal was exposed to noise. An IV cisplatin injection of 8 mg/kg body weight was given 30 minutes after noise exposure. The ABR thresholds were determined 5 days after noise exposure.

THIRD SERIES

This series was used as a control group to study the effect of noise alone on 14 guinea pigs. The animals were unilaterally exposed to noise. The ABR thresholds were determined immediately after noise exposure (2 guinea pigs, TTS), 3 days after (10 guinea

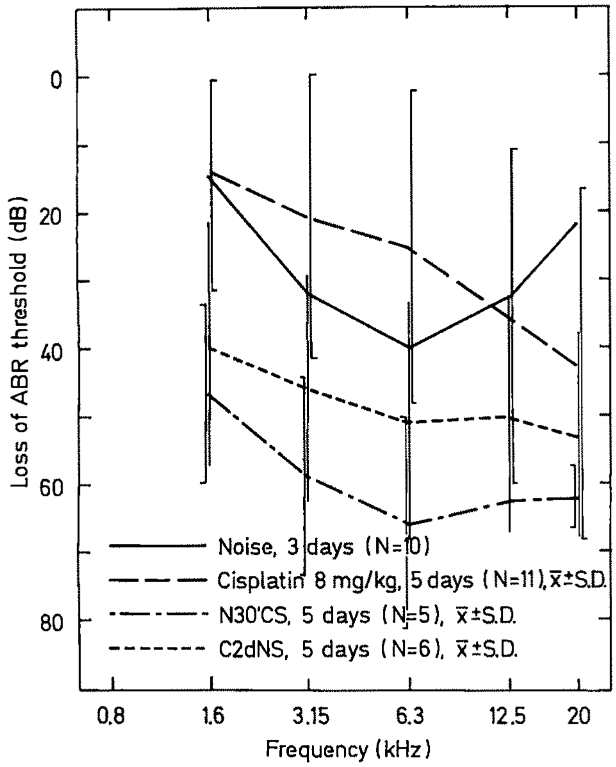

Fig 6. Comparison of temporary interaction effects. Shows mean ABR threshold loss for two groups receiving single intravenous injection of cisplatin at 8 mg/kg body weight in combination with noise exposure.

pigs), and 20 to 26 days after (group N, 10 guinea pigs, PTS).

RESULTS

GENERAL FINDINGS

In groups C2dNL, C3dNL, N30′CL, and N3dCL, administration of cisplatin at 7 mg/kg body weight to 51 guinea pigs resulted in severe adverse effects. Twenty-three animals (45%) died 3 to 14 days (mean 8 days) after the injection. Most of the remaining 28 animals were in good condition after 3 weeks, but 4 animals exhibited a 25% weight loss. The mean weight loss was 2%.

There was no correlation between weight loss and loss of auditory thresholds. A unilateral middle ear infection was found in three guinea pigs from groups C2dNL and N30′CL, as detected by otoscopy and confirmed at autopsy. The results of these ears were excluded.

In groups C2dNS and N30′CS, 3 of the 14 animals receiving cisplatin at 8 mg/kg body weight died. Two of the surviving animals were in fairly poor condition, as indicated by a 25% weight loss 5 days after the injection, at the time of ABR threshold measurement.

AUDITORY FINDINGS

Long-term Follow-up. Administration of an IV injection of cisplatin in a dose of 7 mg/kg resulted in a loss of ABR threshold sensitivity with considerable interindividual variability that could be followed up for a long period in the ear not exposed to noise. The ototoxic effect of cisplatin at 7 mg/kg body weight is shown in Fig 2. (The ABR audiogram corresponds to an ordinary clinical audiogram showing loss of ABR thresholds in relation to ABR thresholds of a control group.) The mean ABR thresholds 2 days (determined for 16 guinea pigs from group C2dNL) and 19 to 26 days (determined for 26 guinea pigs from groups C2dNL, C3dNL, N30′CL, and N3dCL) after the injection are compared. The ABR threshold shifts for 1.6, 3.15, 12.5, and 20 kHz were found to be statistically significantly larger ($p < .05$, one-way analysis of variance [ANOVA]) 2 days as compared to 19 to 26 days after the injection. This observation indicates the existence of a temporary effect.

Exposure to broadband noise (1.5 to 5 kHz) of 137 dB SPL for 30 minutes produced a considerable ABR threshold shift, albeit with great interindividual variability. Figure 3 shows the mean audiograms immediately (determined for 2 guinea pigs from the third series) and at 3 days (determined for 10 guinea pigs from group N3dCL and from the third series) and 20 to 26 days (group N) after noise exposure. The noise-induced ABR threshold shift was most pronounced for the frequencies 3.15, 6.3, and 12.5 kHz. The ABR thresholds remained almost the same from 3 days to about 3 weeks.

The mean audiograms of the ears exposed to noise in groups C2dNL and C3dNL (cisplatin injection before noise exposure) are shown in Fig 4, and compared with the reference audiograms for the cisplatin-induced (from Fig 2) and noise-induced (group N, from Fig 3) threshold shifts, respectively. The threshold shifts for groups C2dNL and C3dNL were rather similar. There was no statistically significant difference between the two groups (one-way ANOVA). When groups C2dNL and C3dNL were amalgamated into group CNL, no statistically significant difference in threshold shift was found between group CNL and group N (one-way ANOVA).

In groups N30′CL and N3dCL (noise exposure before cisplatin injection), all surviving animals (13 altogether) had large shifts of ABR thresholds, with the exception of 1 animal in each group with minor changes for 1.6 and 20 kHz, but considerable changes for the middle frequencies. The mean audiograms for groups N30′CL and N3dNL are shown in Fig 5. Of the two groups, group N30′CL showed the largest shift of ABR thresholds, but this was only statistically significant for 6.3 kHz ($p < .05$, one-way ANOVA). The threshold shift for group N30′CL was found to be statistically significantly larger than that in group N ($p < .05$, one-way ANOVA) for all five frequencies.

The largest threshold shift after combined exposure was achieved when the animals were exposed to noise 30 minutes before the cisplatin injection. The threshold shift for group N30'CL was found to be statistically significantly larger than that in group CNL ($p < .05$, one-way ANOVA) for all five frequencies.

For groups N30'CL and N3dCL an additive effect could be seen for all five frequencies. There was a more than additive effect of ABR threshold change, ie, a potentiation, for group N30'CL for 1.6 kHz ($p < .01$, two-way ANOVA) and for group N3dCL for 1.6 and 20 kHz ($p < .05$, two-way ANOVA). For group CNL a less than additive effect, statistically significant for 3.15 kHz ($p < .05$, two-way ANOVA), was noted.

Short-term Follow-up. In the animals that received an IV injection of cisplatin at 8 mg/kg body weight, considerable interindividual variability of the ABR thresholds in the ear not exposed to noise was found after 5 days. In the ears exposed to noise a smaller variability in both groups could be detected. The mean audiogram of the ears exposed to noise for each group, together with the mean audiogram of those not so treated, is shown in Fig 6. In comparison to Fig 2 it can be seen that the mean ABR thresholds 5 days after an injection of 8 mg/kg cisplatin are in the same range as the ABR thresholds 2 days after the 7-mg/kg injection. A severe shift of ABR thresholds in the ears exposed to noise was found for both groups in the short-term follow-up study. There was no statistically significant difference in threshold shift between the two groups (one-way ANOVA). The combined effects are recorded as greatest for 1.6 kHz, ie, for the frequency at which noise exposure affected the ABR threshold sensitivity least.

DISCUSSION

NOISE-CISPLATIN INTERACTION

The major finding in the present study was the importance of the temporal order of exposure for the combined effects of noise and cisplatin on the electrophysiologic hearing thresholds in the guinea pigs. The greatest response was achieved when the noise exposure preceded the cisplatin administration. No significant potentiation or inhibition was seen when the cisplatin injection was given 2 or 3 days before the noise exposure. The observation of the combined effects of noise and cisplatin is in accordance with an earlier report from Boettcher et al.[9]

GENERAL TOXICITY

Safe therapy with cisplatin requires its delivery to the tumor mass in a concentration within so narrow a range as to be efficacious without unacceptable adverse effects. There is, however, a considerable variation among individuals and experimental animals in the extent to which cisplatin can induce toxic effects. The dose used in the present long-term follow-up, 7 mg/kg body weight by IV injection, caused considerable mortality. It can be expected that the many animals that died were killed by a renal insufficiency induced by cisplatin. Inhibition of the urinary excretion of cisplatin and its breakdown products by renal impairment can cause excessive accumulation, since the urinary tract is the pathway of its elimination. About 3 weeks after the IV injection the mean audiogram of the unexposed ears of the remaining animals indicated a recovery from the cisplatin-induced threshold shift. It has otherwise been shown that there is no direct correlation between cisplatin-induced hearing loss and mortality.[17,24]

POTENTIATION

The threshold shift caused by the broadband noise exposure was predominantly located in the middle frequencies. Nevertheless, the largest effect of the combined administration was seen for the lowest and the highest frequencies, indicating a spread of the combined damage in the cochlea. Studies on iontophoresis of cisplatin into the scala media have revealed a uniform susceptibility of the sensory structures in different regions to the drug.[13] In view of these results one may speculate that the spread of damage in the present study was due to an increased amount of cisplatin in the organ of Corti. Considering the high concentration of cisplatin in the stria vascularis following an IV injection of the drug,[14] a greater influx of cisplatin to the organ of Corti is to be expected if the permeability of the stria vascularis is increased by changes induced by noise.[25]

It could be postulated that noise exposure before cisplatin injection resulted in a potentiation with a permanent impairment of the cochlea. The potentiation was estimated on the ABR threshold shift, and seen as an additive or more than additive summation of the effects of noise and cisplatin.

In the animals exposed to cisplatin before noise, no significant potentiation occurred. A considerable amount of cisplatin ought, however, to remain in the animals at the time of noise exposure 2 and 3 days after the injection, since cisplatin is excreted slowly, at least in humans[26] and in rats.[27]

A time-related susceptibility to cochlear damage from noise and cisplatin was evident. The sequence of exposure was of more significance than the interval between noise exposure and cisplatin injection for the combined effect. However, even the interval was of importance. When the period between noise exposure and cisplatin injection was extended from 30 minutes to 3 days, the combined effects caused a shift of ABR thresholds that was still large, although less pronounced. If the interval had been further prolonged, the interaction might have been still less. When cisplatin was given by multiple low-dose intraperitoneal injections starting 7 to 10 days after noise exposure, no potentiation was observed.[8]

For the groups receiving cisplatin injection before noise exposure, an interval of 2 or 3 days gave the same effect. A simultaneous exposure to noise and cisplatin might be the most hazardous combination.

The combined effect of a broadband noise exposure before an IV injection of cisplatin was most obvious in the long-term follow-up, when an interval of about 3 weeks was used to let the damage stabilize (Fig 1). In the short-term follow-up the combined administration resulted in a severe threshold shift for both groups (noise exposure before cisplatin injection, or vice versa) 5 days after the injection, indicating that the combined effect on the TTS was less influenced by the sequence of exposure. The lack of difference between the two groups could also be the result of a higher dose of cisplatin given to the animals.

Both noise and cisplatin can separately damage the OHCs, but by wholly different mechanisms. The synergistic effect of noise and cisplatin cannot be interpreted as a pharmacodynamic interaction. The mechanism of synergistic interaction must be due to a different process. In animals in which a potentiation was achieved, a synergistic effect could have occurred at the cellular level in the organ of Corti. Although the exact mechanism of the interaction cannot be established from the present study, it must be due to potentiation of cell injury by two different mechanisms.

When comparing different studies on ototoxic drugs and noise it is important to consider the action of the drug on inner ear tissues, the mode of administration, the amount of the dose, the characteristics of the noise exposure, and, according to the present findings, the sequence of exposure. A number of animal experiments have revealed that noise exposure alters the effect of aminoglycosides.[28,29] Kanamycin has been reported to produce a dose- and time-dependent response[30] and to have maximum effects when administered concomitant with noise exposure.[31]

HEARING LOSS PRIOR TO CISPLATIN TREATMENT

To extrapolate findings from an animal experiment to a clinical situation is always hazardous. There is unlikely to be any risk of a potentiation in the auditory system for patients treated with cisplatin in a hospital and thereafter exposed to unwanted noise. On the other hand, patients extensively exposed to noise just before hospitalization and during cisplatin treatment may theoretically run an increased risk of developing hearing loss in connection with their therapy.

In light of a previous experimental study in which a noise-induced hearing loss prior to cisplatin treatment was not found to increase the ototoxic effect of cisplatin,[8] the present result demonstrates the complexity of noise-drug interactions. The lack of potentiation in that study could be attributed to the fact that the noise exposure preceded the cisplatin treatment by 7 to 10 days, which allowed a major healing of the damage to the inner ear structures. Moreover, several clinical studies have failed to show that the ototoxic effect of cisplatin increases with a prior stable hearing loss.[4,6,7,32]

Sensorineural hearing loss is caused by numerous factors, and there is no study available about cisplatin treatment of patients with prior hearing loss caused primarily by occupational noise. Potentiation between noise and cisplatin treatment is unlikely to be an important factor in explaining individual susceptibility to cisplatin ototoxicity. Potentiation of noise and cisplatin must, however, be considered, and protection of the hearing function from excessive noise during chemotherapy with this drug is advisable.

CONCLUSIONS

The results from the long-term follow-up show that the combined effects of noise exposure and cisplatin are dependent on both the timing of the exposure and the interval between the exposures. A potentiation of noise and cisplatin was achieved when cisplatin was given by a bolus injection of 7 mg/kg body weight either 30 minutes or 3 days after broadband noise exposure. Since in the short-term study the combined effects were not influenced by the sequence of exposure, different effects on TTS and PTS are indicated. Therefore, it is important to protect the ear against noise during cisplatin therapy.

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MAXILLARY SINUS ATELECTASIS

PATRICK J. ANTONELLI, MD
MINNEAPOLIS, MINNESOTA

ARNDT J. DUVALL III, MD
MINNEAPOLIS, MINNESOTA

STEVEN L. TEITELBAUM, MD
ST LOUIS, MISSOURI

Two patients are presented with maxillary bone loss and atelectasis of the sinus walls in association with chronic subclinical maxillary sinusitis. Maxillary sinus atelectasis results in a mild cosmetic deformity, but may also cause diplopia by involving the orbital floor. Ostial obstruction and inflammation-mediated osteopenia are postulated to be the responsible mechanisms. Surgical treatment of the sinusitis may prevent progression of the bone loss.

KEY WORDS — atelectasis, maxillary sinus, sinusitis.

INTRODUCTION

The sequelae and complications of sinusitis that have been reported are primarily suppurative.[1] Asymptomatic maxillary bone loss with atelectasis of the maxillary sinus is not widely recognized as a sequela of chronic maxillary sinusitis, even when there is associated osteomyelitis with demineralization.[2] The purpose of this paper is to describe two patients who presented with atelectasis of the maxillary sinus in association with only subclinical chronic sinusitis, and to offer insight into the possible causative mechanisms.

CASE REPORTS

Case 1. A 32-year-old man developed excruciating pain in his right upper teeth during a pressurized commercial airplane flight. He was without further symptoms until a few days later. While he was watching television, the right side of his face felt unusual. On inspection, he felt that his right cheek was depressed. He did not have any facial pain, symptoms referable to the sinuses, or vision changes, such as diplopia. He did not seek medical evaluation until approximately 1 year later. Computed tomograms of the face revealed collapse of the anterior, posterior, and medial walls of the right maxillary sinus (Fig 1); hence, the patient was referred to the otolaryngology service. The dentition was healthy and the occlusion was subjectively unchanged. The facial and trigeminal nerves were symmetrically intact. No enophthalmos was apparent. The remainder of the head and neck examination yielded unremarkable findings.

The medical history was significant for pulmonary tuberculosis that was treated for 1 full year, ending approximately 1 year prior to presentation to the otolaryngology service. Following the treatment for tuberculosis, the patient was treated for asthma with bronchodilators. He had no history of nasal polyps or chronic sinusitis, but did suffer one episode of bilateral acute sinusitis 2 years prior to presentation that was radiographically confirmed and responded well to oral antibiotics and nasal decongestants.

Sinus endoscopy revealed lateral bowing of the right lateral nasal wall. Exploration of the right maxillary sinus through a Caldwell-Luc operation revealed no erosive lesions. The anterior maxillary wall bone was very thin and bowed posteriorly, but with-

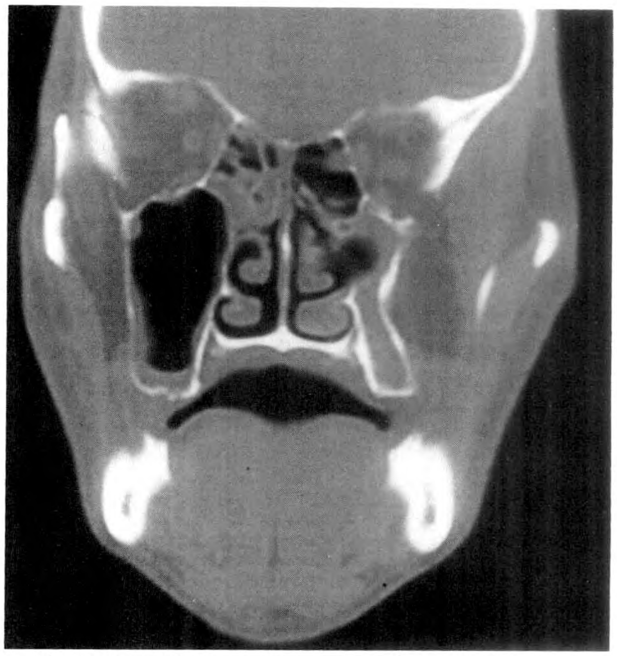

Fig 1. (Case 1) Computed tomogram of paranasal sinuses.

From the Department of Otolaryngology, University of Minnesota School of Medicine, Minneapolis, Minnesota (Antonelli, Duvall), and the Department of Pathology, Jewish Hospital at Washington University School of Medicine, St Louis, Missouri (Teitelbaum).

REPRINTS — Patrick J. Antonelli, MD, Box 396 UMHC, 420 Delaware St SE, Minneapolis, MN 55455.

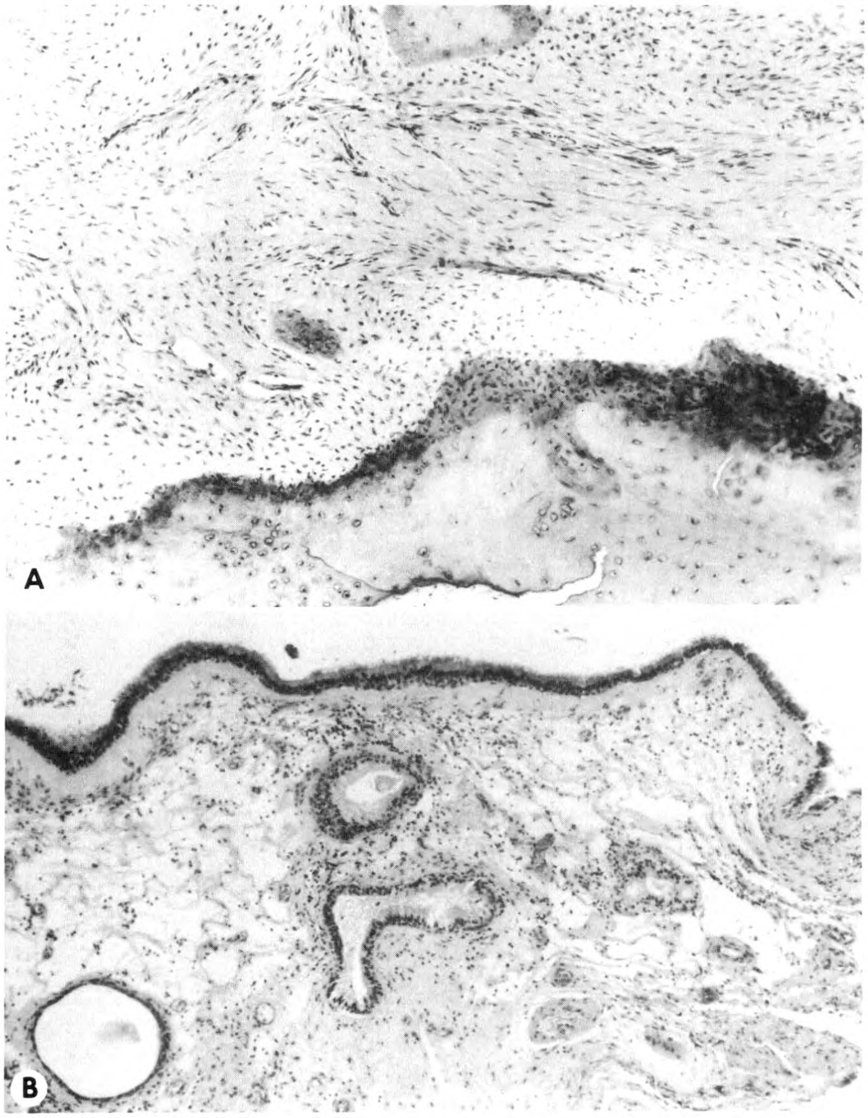

Fig 2. (Case 1) Photomicrographs. A) Right maxillary sinus bone appears normal. B) Overlying mucosa is inflamed.

out signs of necrosis. The antrum was collapsed and lined with pale, edematous mucosa. Histopathologic examination revealed normal-appearing bone in a fibrocellular stroma and chronic inflammation of the mucosa (Fig 2). Cultures of sinus bone and mucosa revealed normal oral flora and no bacterial or fungal pathogens. No additional treatment was prescribed. The patient has failed to keep follow-up appointments, but his family reports that he is doing well, without additional symptoms or facial changes, 6 months postoperatively.

Case 2. A 65-year-old man presented to the otolaryngology service with a 2-month history of gradual left cheek depression and bilateral nasal obstruction since childhood, but no other symptoms referable to the nose or sinuses. His medical history was significant for routine dental extractions, prostate cancer that was treated by radical prostatectomy 2 years prior to presentation, type II diabetes mellitus, remote alcohol abuse, and coronary artery disease. Examination revealed an obvious depression of the left cheek, just below the infraorbital rim. Anterior rhinoscopy was limited by a bilateral septal deviation, more marked on the left. Flexible nasal endoscopy revealed fullness in the left middle meatus, but no erosive lesions or discrete tumors. A left anterior maxillary wall defect and atrophic lateral buttress were palpable transorally. The palate was intact and the left maxillary canine and premolar were secure. Facial and trigeminal nerve function was symmetrically intact.

Sinus films taken 3 months prior to presentation were interpreted by a radiologist as normal, but revealed bone loss of the left lateral buttress. Sinus films taken on the initial otolaryngologic evaluation confirmed this finding. Axial computed tomograms with coronal reconstruction showed collapse of the anterior, posterior, and superior maxillary sinus walls; however, no tumor was identified in or around the sinus (Fig 3). A bone scan, done just prior to presen-

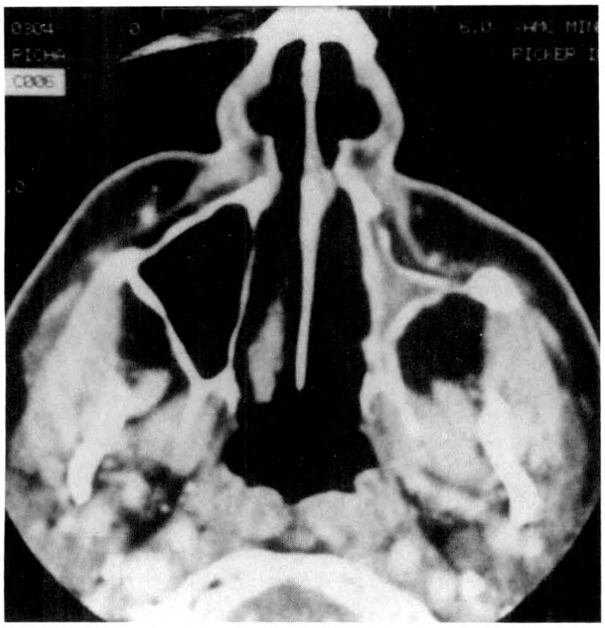

Fig 3. (Case 2) Computed tomogram of paranasal sinuses.

tation in follow-up for the prostate cancer, was interpreted as normal.

A Caldwell-Luc operation was performed. The bone of the entire maxillary sinus was extremely thin and soft, but was without necrosis or erosions. The sinus mucosa was pale and no pus was seen. A polyp measuring 10 x 8 x 5 mm was removed from the floor of the sinus. Polypoid mucosa was also removed from the area surrounding the natural ostium. Microscopic examination revealed unremarkable bone (Fig 4A). There was chronic mucosal inflammation and marked stromal edema with plasma cell infiltrate in the polyp (Fig 4B).

No additional treatment was prescribed and the patient is doing well 6 months postoperatively.

DISCUSSION

Occult maxillary bone loss is a potentially ominous radiographic finding, as the diagnosis is carcinoma until proven otherwise.[2] Maxillary bone loss may result from many disease processes. Unfortunately, the clinical history and objective findings do not always suggest the underlying cause for the bone loss. For instance, osteomyelitis, which results in focal bone loss, most often develops from an odontogenic infection,[3,4] but may occur in the absence of oral disease or local trauma.[2,4] Rare disorders, such as massive osteolysis, or phantom bone syndrome, also result in asymptomatic maxillary bone loss.[5] These asymptomatic and unusual causes of maxillary bone loss generally require histologic examination to establish a diagnosis.[6]

Sinusitis is one of the most common diseases that can cause maxillary bone loss in Western populations. Acute sinusitis usually results in a lytic osteitis, whereas low-grade repeated infections are more commonly associated with a blastic osteitis.[7] Chronic osteolytic sinusitis resulting from inhaling cocaine has been reported.[8] Maxillary mucoceles, which are thought to result from chronic or recurrent sinusitis, rarely result in bony erosion.[9] When the roof of the maxillary sinus is eroded by a mucocele, enophthalmos may develop.[10]

Chronic sinusitis as a cause of maxillary bone loss and collapse of the sinus walls has been reported previously. In 1981, Wilkins and Kulwin,[11] ophthalmologists, described five patients who developed spontaneous collapse of the orbital floor and enophthalmos in the presence of chronic or recurrent sinusitis. All of these patients had a long history of maxillary sinusitis or allergic rhinitis. None were described as having sinus atelectasis. In 1986, Wesley et al[12] presented a similar case in the otolaryngologic literature. In 1991, Isaacs et al[13] described two patients who developed enophthalmos and atelectasis of the maxillary sinus in association with chronic subclinical sinusitis. Both of the patients whom we have presented developed maxillary sinus atelectasis, without clinical evidence of enophthalmos. In both of our patients, the historical and histologic data suggested that the sole cause for the maxillary sinus atelectasis was mild chronic maxillary sinusitis.

Obstruction of the sinus ostium may be the critical factor in the development of maxillary sinus atelectasis. Ostial obstruction is thought to be the principal factor in the initiation of both acute and chronic sinusitis.[14] The first patient's history of maxillary pain during an airplane flight shortly before he noticed the depression in his cheek was presumably a result of change in environmental pressure. This indicates that some degree or period of the sinus ostial obstruction was present prior to the "collapse" of the sinus. Local stress is known to influence the remodeling of bone.[15] Since bone mass is ultimately a reflection of the remodeling process, changes in the rate of remodeling can theoretically cause collapse of the sinus walls. In this regard, both patients with maxillary collapse had evidence for maxillary bone loss.

Ostial obstruction with development of negative pressure may serve as an example of a bone resorptive agonist, as pressure changes have been shown to result in bone resorption in vitro.[16] It is well recognized that a pressure difference between the sinuses (or middle ear) and the environment causes pain. The absence of notable symptoms in both patients suggests that minimal or transient negative pressure was

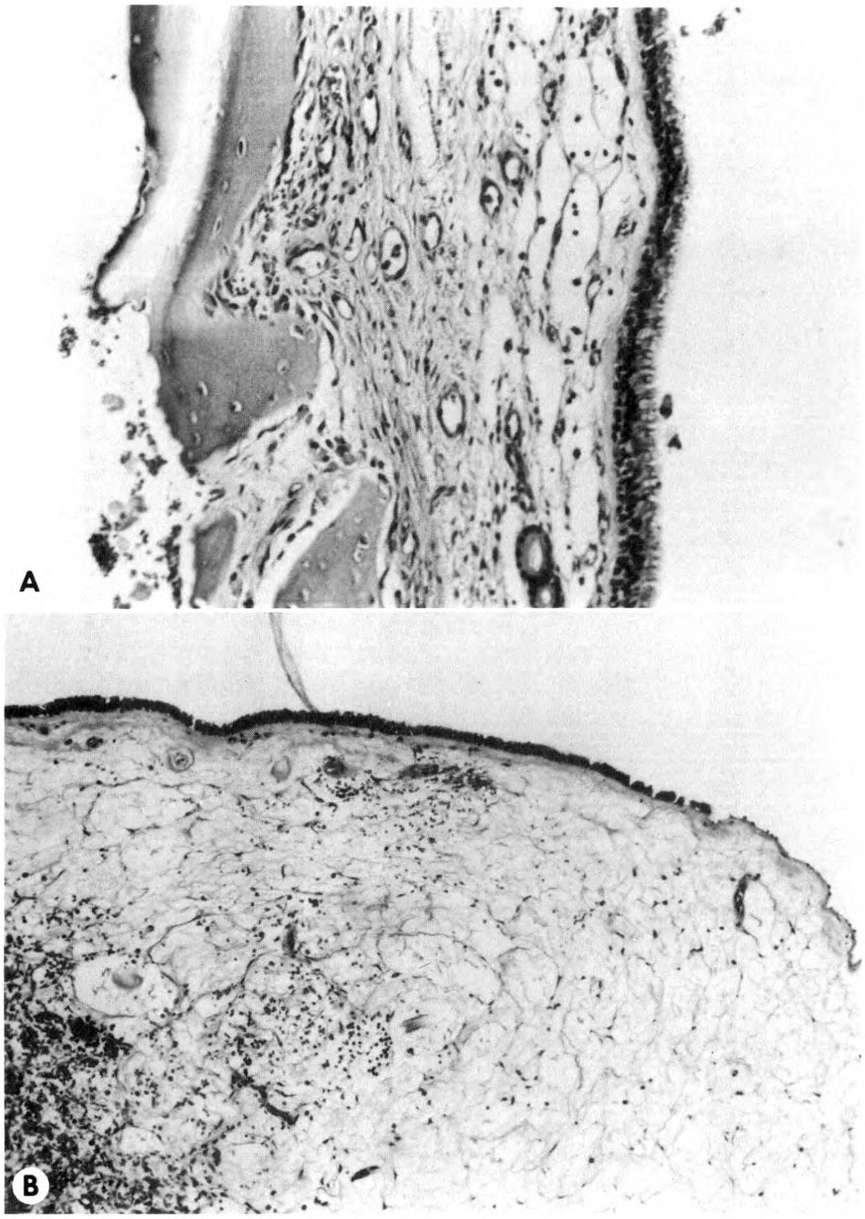

Fig 4. (Case 2) Photomicrographs. A) Left maxillary sinus bone and mucosa are unremarkable. B) Antral polyp has marked stromal edema and plasma cell infiltrate.

necessary to develop sinus collapse. Hence, it is unlikely that a pressure differential was the only causative mechanism.

Because inflammation is known to promote osteopenia,[17] chronic maxillary sinusitis may have prompted the bone loss. Cytokines produced by inflammatory cells might mediate the bone loss in inflammation-mediated osteopenia by inhibiting osteoblast cell replication and collagen synthesis[18,19] and/or stimulating bone resorption.[20] Osteoblasts, as well as immunocompetent cells, produce cytokines, and their production is modulated by other cytokines.[21] Thus, the regulation of cytokine-mediated bone metabolism is a complex process, but one that is receiving increased attention.

In both patients presented in this paper, the bone loss was limited to the maxilla, and the only local abnormality was chronic sinusitis. The absence of increased osteoclastic activity suggests that the bone loss is most likely a result of decreased bone formation, as seen in inflammation-mediated osteopenia. Hence, inflammation-mediated osteopenia may have a role in the development of maxillary sinus atelectasis.

If maxillary sinus atelectasis is caused by chronic subclinical sinusitis, traditional treatment modalities for chronic sinusitis could be expected to arrest or reverse the disease process. For diagnostic purposes, we performed a Caldwell-Luc operation on both patients, and each has done well for at least 6 months.

It is not clear why maxillary sinus atelectasis developed in these two patients, and not in many other patients with chronic maxillary sinusitis. These patients may represent extreme cases along a spectrum, with less dramatic maxillary sinus collapse not being recognized clinically or radiographically. Alternatively, sinus atelectasis may reflect an unusual biologic response to inflammation. In order to determine the pathogenesis and optimal treatment for maxillary sinus atelectasis, further investigation into the metabolism of maxillary bone in the presence of sinus inflammation is necessary.

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THE PROSPER MENIERE SOCIETY

The annual meeting of the Prosper Meniere Society will be held in Aspen, Colorado, February 21-28, 1993. For more information, please contact Apryl Salz or Jane Wells, Meeting Coordinatos, c/o I. Kaufman Arenberg, MD, FACS, Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone 303-850-9545; fax 303-788-4234.

Ann Otol Rhinol Laryngol 101:1992

ULTRASTRUCTURAL CHANGES IN HUMAN NASAL CILIA CAUSED BY THE COMMON COLD AND RECOVERY OF CILIATED EPITHELIUM

MARKUS RAUTIAINEN, MD
TAMPERE, FINLAND
HEIKKI KIUKAANNIEMI, MD
OULU, FINLAND
JUHANI NUUTINEN, MD
KUOPIO, FINLAND
YRJÖ COLLAN, MD
TURKU, FINLAND

Changes in the ultrastructure of human respiratory cilia caused by the common cold were studied in 12 patients. The nasal mucosa was studied three times: on the first or second day after the beginning of symptoms, and 1 week and 3 weeks after the first biopsy. The damage was most severe at 1 week. The most remarkable finding was the loss of cilia and ciliated cells. However, the ultrastructure was usually normal, without any increase in tubular anomalies, as compared with the normal material of the previous reports. Three weeks after the beginning of the disease the number of cilia and ciliated cells had increased to nearly normal. However, as a sign of regeneration, immature short cilia (0.7 to 2.5 μm in length) were often seen. The ciliary orientation was uniform, dynein arms were normal, and there was no increase in the number of tubular anomalies. The results suggest that the impaired mucociliary function during viral infections is due to the loss of cilia and ciliated cells, rather than to ultrastructural anomalies in the cilia. The development of tubular anomalies and random ciliary orientation may require more extensive exposure to factors affecting ciliary function.

KEY WORDS — ciliary ultrastructure, mucociliary function, respiratory infection, viral infection.

INTRODUCTION

The common cold[1] is an important but complex infectious syndrome caused by a large number of different viruses.[2] Acute viral infections may lead to chronic respiratory diseases, and bacterial infections in the upper or lower respiratory tract are usually preceded by acute viral infections.

Many kind of defects in ciliary ultrastructure have been reported in recurrent or chronic respiratory infections,[3-6] in asthma,[7] and in allergic rhinitis.[8] There is little doubt that viral infections of the respiratory tract can disturb mucociliary function.[9,10] Experimentally, the reduction of mucociliary clearance during viral infection has been found to be due to ciliary disorders, a decrease in the number of cilia, and decreased ciliary beat frequency.[11]

This study deals with the abnormalities of the ciliary ultrastructure on nasal respiratory epithelium in patients suffering from the common cold, and the regeneration of ciliated epithelium.

PATIENTS AND METHODS

Sixteen volunteers — nonsmoking national servicemen — were selected for this study. The patients were selected on the clinical basis of respiratory symptoms without any culture of respiratory viruses. At the time of the study there was no viral epidemic in the environment of the patients. They all had symptoms of acute common colds with acute watery rhinitis and nasal blockage for 1 to 2 days. They had a mild fever (body temperature 37.5°C to 38.5°C), but were otherwise healthy and without any history of respiratory allergy. All underwent clinical examinations by an otolaryngologist, and none had any signs of bacterial infection. After informed consent, local anesthesia was induced with cotton pieces moistened with 4% lidocaine hydrochloride with epinephrine, and a specimen for electron microscopy was taken from the middle turbinate of the nasal cavity. The first specimen was taken at the time of diagnosis, usually on the first or second day from the beginning of symptoms. The second specimen was taken 1 week later, and a third sample was taken 3 weeks after the first biopsy.

During the study, no antibiotics or local nasal drugs were used. All the patients recovered in a week and had been subjectively healthy for 2 weeks before the third specimen was taken. The study plan was approved by the institutional review board for human studies at Pohja Military Hospital.

Samples for electron microscopy were fixed with 1% glutaraldehyde and 4% formaldehyde fixative in 0.1 mol/L phosphate buffer at 4°C for 1 week. The

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From the Departments of Otolaryngology and Pathology, Kuopio University Hospital, Kuopio (Nuutinen, Rautiainen), the Department of Otolaryngology, Tampere University Hospital, Tampere (Rautiainen), the Department of Otolaryngology, Pohja Military Hospital, Oulu (Kiukaanniemi), and the Department of Pathology, Turku University, Turku (Collan), Finland.

REPRINTS — Juhani Nuutinen, MD, Dept of Otolaryngology, Kuopio University Hospital, SF-70210 Kuopio, Finland.

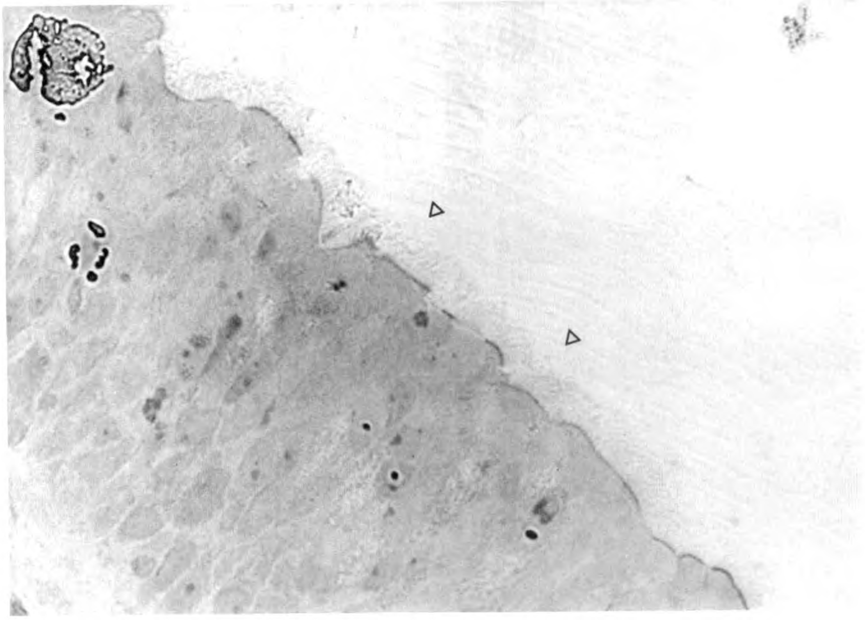

Fig 1. Phase-contrast micrograph of nasal mucosa sampled at beginning of disease (original x187.5). Normal amount of cilia (arrowheads).

samples were then washed in veronal acetate hydrochloride buffer (pH 7.4), postfixed for 1 hour with osmium tetroxide in *S*-collidine buffer (pH 7.4), washed again in veronal acetate hydrochloride buffer, and stained en bloc with uranyl acetate in veronal acetate hydrochloride buffer. The samples were embedded in Epon 812 and were sectioned with a diamond knife. Ultrathin sections were stained with uranyl acetate–lead citrate[12] and examined in a Jeol JEM 100 S electron microscope in random order.

Finally, there were 12 patients in whom all three biopsy specimens were technically good enough for analysis. From the specimens the areas with the best cross sections of cilia were chosen, and electron micrographs were exposed at the primary magnification x15,000. The final magnification of the prints was x45,000. Ciliary orientation was estimated by measuring the standard deviation of the angles between the plane defined by the central tubules and a reference line, by means of a semiautomatic image

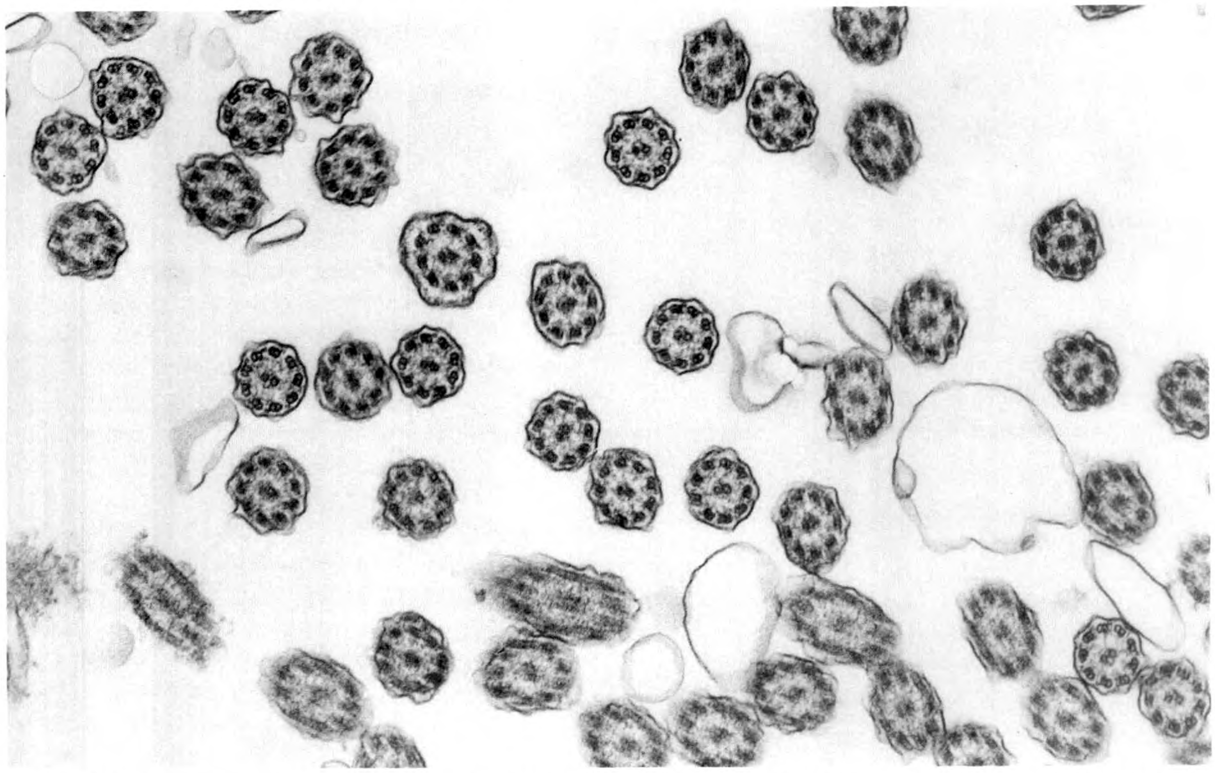

Fig 2. Electron micrograph of mucosa sampled at beginning of disease (original x45,000). Ciliary cross sections are uniformly normal.

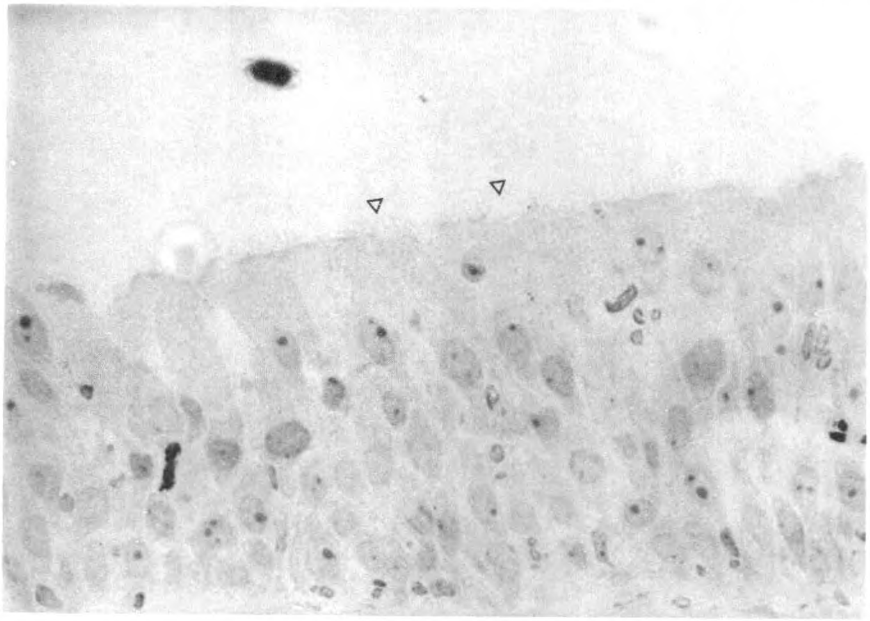

Fig 3. Phase-contrast micrograph of mucosa sampled 1 week after onset of disease (original x187.5). Arrowheads — loss of cilia.

analyzer (IBAS I).[13]

RESULTS

Biopsy specimens taken at the time of the diagnosis revealed a normal number of cilia in 10 of 12 patients. The number of cilia was reduced in 2 patients. However, most specimens revealed almost normal ciliary ultrastructure with a normal amount of compound cilia, some tubular abnormalities, and occasional local ciliary disorientation (Figs 1 and 2). Most cells in the samples were ciliated, and in the ultrastructural sections we usually found a number of ciliary cross sections.

In the samples taken 1 week after the beginning of symptoms, the epithelial cells were mostly without cilia or with only a few cilia (Figs 3 and 4). Only in two patients were cells found with the normal number of cilia.

In the last biopsies, 3 weeks after diagnosis, the surface of the epithelium was usually ciliated, and the sections for electron microscopic study showed a normal number of ciliary cross sections in seven patients and a reduced number in two patients. In three patients, only a few cilia were found.

Many kinds of tubular anomalies were found in the biopsy specimens at all three intervals. However, the tubular anomalies were seen only in a small percentage of cilia, and we did not find any difference between the degree of these anomalies in the different groups. The same number of compound cilia was found in all of the groups. Also, dynein arms were usually present and appeared to be of normal length at all three time periods.

The ciliary orientation was usually very uniform in all samples. The mean of the SD of the ciliary orientation was 30.8° (range 21.9° to 37.9°) in the first biopsy, 29.6° (range 15.7° to 42.1°) after 1 week, and 24.1° (range 17.4° to 33.2°) after 3 weeks. In some specimens taken at the time of diagnosis, we found local ciliary disorientation, but the main orientation in these samples was uniform.

In longitudinal sections of specimens taken 3 weeks after diagnosis, we found some cilia shorter than normal in four patients. The length of these short cilia varied between 0.7 μm and 2.5 μm (Fig 5). The same kind of cilia were found in only one specimen taken after a week of the disease, and in no samples taken initially.

DISCUSSION

During the first days of a common cold, the changes on the nasal mucosa seemed to be slight. The degree of ultrastructural pathologic findings of the cilia was essentially the same as reported in normal controls.[14] The most severe damage was seen in the samples taken 1 week after the beginning of symptoms. The main finding in these samples was the loss of cilia and ciliated cells. The same kinds of results were reported by Sakakura et al,[11] who studied ciliary injury on the nasal epithelium of chickens with scanning electron microscopy during experimentally caused Newcastle disease virus infection. Their results showed that the peak of mucociliary clearance reduction was on the seventh day of infection, and the maximum loss of cilia was on the fifth day. Also, the results of Winther et al[15] showed some sloughing of epithelial cells but no destruction of epithelial lining in patients with naturally occurring common colds. A more marked feature than the loss of cilia was local neutrophilia of

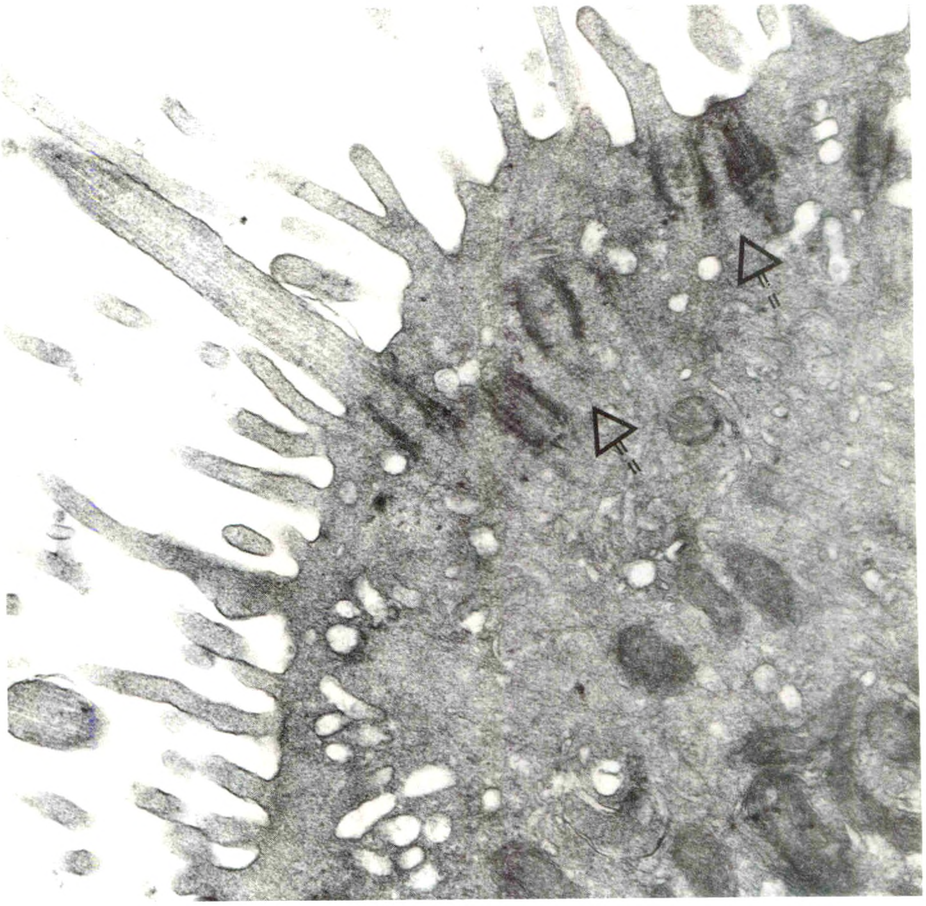

Fig 4. Electron micrograph of nasal mucosa sampled 1 week after onset of disease (original x45,000). This section has only one cilium. There are several basal bodies within cell membrane (arrows).

the nasal mucosa.[15] Carson et al[16] studied defects caused by acute viral respiratory infection in nasal ciliated epithelium in children. Their results showed a focal loss of cilia during the first week of illness. They also reported a clearly elevated number of tubular anomalies in the cilia. In our present study the number of abnormal axonemal structures can be considered normal at different periods during the illness, and the loss of cilia is markedly more pronounced than in the study of Winther et al.[15]

In the samples taken 3 weeks after the beginning of the disease, the amount of cilia and ciliated cells was normal or almost normal in 9 of 12 patients. However, as a sign of regeneration, some short, immature cilia were seen in many samples of four patients. Longitudinal sections of the cilia were not systematically made. However, no short cilia were seen in longitudinal sections in samples taken at the beginning of the disease. In the series of Carson et al,[16] the fine structure of the cilia gradually returned to normal within 6 weeks. In the organ culture of ciliated cells from patients with cystic fibrosis, the ciliogenesis was nearly complete within 1 month of injury, but there were still some short cilia.[17] In this study the ultrastructure usually revealed the normal 9 plus 2 arrangement,[18] and we did not notice any increase of tubular anomalies in the axonemes. It seems that acute viral infection on the respiratory epithelium does not disturb ciliogenesis very much. On the other hand, there may be a chronic condition in which human respiratory cilia are constantly short and a cause of impaired mucociliary transport.[19]

An elevated number of many kinds of tubular anomalies has been reported to be associated with primary ciliary dyskinesia and many other chronic respiratory diseases.[3,20] In the present study an elevated number of tubular anomalies in the ciliary ultrastructure could not be seen at different phases of the illness. The development of ciliary anomalies seems to require a longer exposure to infection or some other agent. Random ciliary orientation has been reported in primary ciliary dyskinesia[21] and also in other chronic respiratory diseases.[22] This study shows that naturally occurring acute viral respiratory infection does not necessarily disturb ciliary orientation, and that it cannot be solely responsible for decreased ciliary function on this basis.

Viral infections are known to impair mucociliary function. Experimentally induced rhinovirus infection in healthy volunteers decreased nasal mucociliary transport at 12 hours postinoculation, with a maximum depression after 3 days. The mean transport rate was slower than normal for 9 to 11 days.[10] Also, an

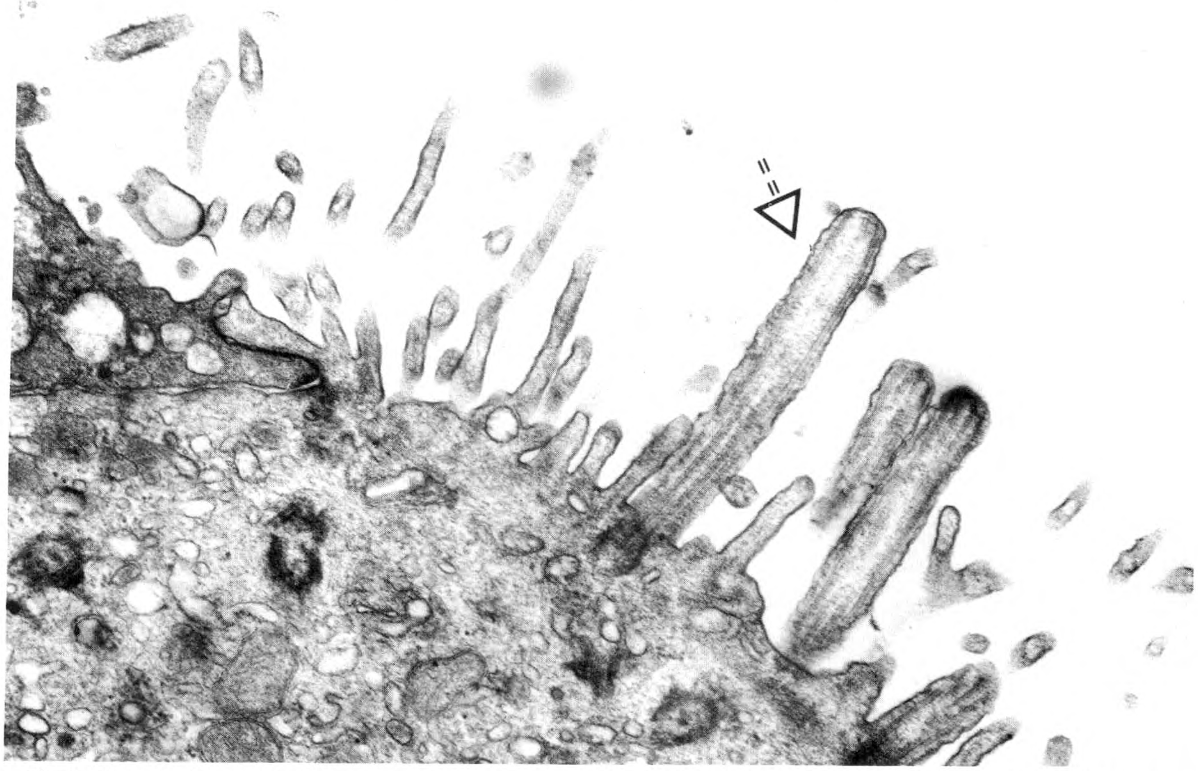

Fig 5. Electron micrograph of mucosa sampled 3 weeks after beginning of disease (original x45,000). Short cilia are sign of ciliogenesis. Arrow — cilium with length of 1.5 μm.

experimental cold caused by Newcastle disease virus in chickens showed a loss of cilia and impaired mucociliary transport of the nasal mucosa.[23] However, mucociliary transport may occur without complete ciliation of the whole epithelial surface. Therefore, the impaired mucociliary function may partly be caused by impaired ciliary motility or coordination. Many inflammatory substances released during infection are ciliostatic,[24] and they may have an influence on the viscoelastic properties of respiratory mucus. Further studies on the molecular basis of ciliary function are needed for further analysis of functional and structural changes in cilia in respiratory disease. Such studies could potentially expose vistas for more directed clinical treatment of respiratory infections.

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28TH POSTGRADUATE COURSE IN EAR SURGERY

The 28th Postgraduate Course in Ear Surgery will be held April 18-23, 1993, in Nijmegen, the Netherlands. For further information and registration form, please write to Prof Dr P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax: 080-540251.

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AMERICAN DIOPTER AND DECIBEL SOCIETY

The American Diopter and Decibel Society will hold its biennial meeting January 16-23, 1993, at the Westin Camino Real in Puerto Vallarta, Mexico. Abstracts are currently being accepted. For further information, contact Robin L. Wagner, American Diopter and Decibel Society, 3518 Fifth Avenue, Pittsburgh, PA 15213; fax (412) 647-8720, phone (412) 647-2227.

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DIAMETER OF THE COCHLEAR NERVE IN DEAF HUMANS: IMPLICATIONS FOR COCHLEAR IMPLANTATION

JOSEPH B. NADOL, JR, MD WEN-ZHUANG XU, MD

BOSTON, MASSACHUSETTS

Although the parameters that are most important for postoperative speech perception in cochlear implantation have not been identified, it is assumed that the numbers of remaining cochlear neurons and spiral ganglion cells in the implanted deaf ears are critical. In this study, we evaluated the correlation of the maximum diameter of the cochlear and vestibular nerve trunks with the number of spiral ganglion cells in horizontal sections of the temporal bone of 42 patients who were profoundly deaf during life, and in 5 patients with normal hearing. The maximum diameters of the cochlear, vestibular, and eighth cranial nerves were significantly smaller in the deaf population as compared to normal-hearing controls. In addition, the counts of the remaining spiral ganglion cells were significantly correlated with the maximum diameter of the cochlear ($p = .0006$), vestibular ($p = .001$), and eighth cranial nerves ($p = .0003$). The regression equation estimated that 25% of the variance of the spiral ganglion cell count was predicted by the maximum diameter of the eighth nerve. Although the results of this study suggest that preoperative radiographic imaging of the diameter of the eighth nerve may be helpful in predicting the residual spiral ganglion cell count, the wide variability of diameters of the eighth nerve in hearing and deaf subjects militates against this theoretic usefulness.

KEY WORDS — cochlear implant, cochlear nerve.

INTRODUCTION

Considerable variability has been demonstrated in postoperative speech perception in individuals who have undergone cochlear implantation.[1] Although all the parameters that may influence postoperative speech perception have not been identified, it is assumed that the numbers of cochlear neurons and spiral ganglion cells remaining in deaf inner ears are of critical importance.[2-5] Several histopathologic studies have demonstrated large variability of the spiral ganglion cell counts in deaf ears.[2,3,5-9] Although the spiral ganglion cell count seems to correlate with several clinical parameters such as age, duration of deafness, and cause of deafness, even within diagnostic categories there is a wide variability of residual spiral ganglion cells.[5] In an effort to prognosticate postoperative success as measured by speech perception in candidates for cochlear implantation, most authors have studied various parameters of preoperative electrical evoked responses or psychophysical testing.[10,11]

Modern imaging techniques, particularly magnetic resonance imaging, are capable of demonstrating the soft tissue contents of the internal auditory canal. The present study was designed to evaluate the relationship between the diameter of the auditory and vestibular nerves and the number of remaining spiral ganglion cells in temporal bones from deaf individuals as evaluated in horizontal sections of temporal bones prepared for light microscopy. We speculated that if the diameters of the auditory nerve or eighth cranial nerve were strongly correlated with the number of spiral ganglion cells, measurement of these structures by preoperative imaging techniques might prove to be a valuable prognostic tool.

MATERIAL AND METHODS

Forty-seven temporal bones from the collection of the Massachusetts Eye and Ear Infirmary were analyzed in this study. Forty-two specimens were from patients with a clinically documented history of profound deafness, and five were from patients with normal hearing. Only one temporal bone per individual was evaluated. For each ear, the age at death, duration of hearing loss, duration of deafness, and otologic diagnosis were documented.

The temporal bones were processed for histologic study as previously described.[12] Temporal bones were sectioned at a thickness of 20 μm in the horizontal plane. Every 10th section was stained with hematoxylin and eosin and mounted on a glass slide. The organ of Corti and spiral ganglion were graphically reconstructed in two dimensions by a method described by Schuknecht[13,14] and Otte et al.[3]

To determine the total spiral ganglion cell count, all ganglion cells with visible nucleoli were counted on every 10th section. Counts were multiplied by 10 to account for unmounted sections, and also by a cor-

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From the Department of Otology and Laryngology, Harvard Medical School, and the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. Supported by grant PO1 DC00361 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

REPRINTS —Joseph B. Nadol, Jr, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114-3096.

TABLE 1. DISTRIBUTION OF DATA SET

Diagnosis	*No. of Temporal Bones*	*Mean Age at Death (y)*
Postnatal viral labyrinthitis	6	53
Congenital rubella syndrome	2	12
Sudden idiopathic deafness	3	57
Bacterial labyrinthitis	5	69
Tumor of temporal bone or cerebellopontine angle	5	41
Otosclerosis and/or presbycusis	2	50
Congenital or genetic cause	8	35
Trauma or fracture of temporal bone	3	53
Aminoglycoside ototoxicity	6	54
Meniere's disease	1	76
Unknown cause	1	73
Normal hearing	5	41
Total	47	

rection factor of 0.9.[15] The total spiral ganglion cell count was also expressed as a percentage of normal as compared to age-matched controls.[3]

The diameters of the cochlear nerve and vestibular nerve were measured at the point of maximum diameter of each nerve within the internal auditory canal in serial horizontal (axial) sections. The maximum diameter of the eighth cranial nerve was estimated by addition of the measured maximum diameters of the auditory and vestibular divisions.

The maximum diameters of the cochlear, vestibular, and eighth cranial nerves were evaluated for correlations with the total spiral ganglion cell count, percentage of normal spiral ganglion cell count for age, percentage of remaining hair cells, percentage of remaining pillar cells, age at death, sex, duration of hearing loss, duration of deafness, and finally, cause of deafness. Statistical analysis was performed with the Pearson correlation coefficient, analysis of variance, the *t* test, and SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

The distribution and mean age at death of the study population are shown in Table 1. With the *t* test (Table 2), it was apparent that the total spiral ganglion cell count and maximum diameters of the cochlear, vestibular, and eighth cranial nerves were all significantly smaller in the deaf population than in the normal-hearing control group. However, the ranges for each parameter demonstrated considerable overlap between hearing and deaf groups.

The Pearson correlation coefficients for the diameters of the cochlear, vestibular, and eighth nerves and various clinical and histopathologic parameters are shown in Table 3. As would be expected, there was no statistically significant correlation between the maximum diameter of the nerves and the side of

TABLE 2. CORRELATION OF SPIRAL GANGLION CELL COUNT AND NERVE DIAMETERS WITH HEARING STATUS (*T* TEST)

	Normal-Hearing (n = 5)		*Deaf (n = 42)*
Spiral ganglion cell count			
Mean ± SD	27,304 ± 4,203		15,463 ± 7,838
Range	23,103 to 31,932		0 to 29,997
p		.0008	
Maximum diameter of cochlear nerve (mm)			
Mean ± SD	1.04 ± 0.11		0.81 ± 0.15
Range	0.90 to 1.20		0.50 to 1.20
p		.0067	
Maximum diameter of vestibular nerve (mm)			
Mean ± SD	0.98 ± 0.08		0.76 ± 0.12
Range	0.90 to 1.10		0.50 to 1.00
p		.0019	
Maximum diameter of eighth cranial nerve (mm)			
Mean ± SD	2.02 ± 0.08		1.57 ± 0.26
Range	1.90 to 2.10		1.00 to 2.10
p		.0001	

TABLE 3. PEARSON CORRELATION COEFFICIENTS FOR DIAMETER OF COCHLEAR AND VESTIBULAR NERVES AND CLINICAL AND HISTOPATHOLOGIC PARAMETERS

	Maximum Diameter of Cochlear Nerve			*Maximum Diameter of Vestibular Nerve*			*Maximum Diameter of Eighth Cranial Nerve*		
	Pearson Correlate	*p*	*n*	*Pearson Correlate*	*p*	*n*	*Pearson Correlate*	*p*	*n*
Left versus right ear	0.06520	.6632	47	0.03773	.8012	47	0.05656	.7057	47
Male versus female	−0.00579	.9692	47	−0.17001	.2533	47	−0.08590	.5659	47
Age at death	−0.06339	.6721	47	−0.00088	.9953	47	−0.03762	.8018	47
Duration of hearing loss	−0.21351	.1496	47	−0.21774	.1415	47	−0.23094	.1183	47
Duration of deafness	−0.21805	.1409	47	−0.22572	.1271	47	−0.23747	.1080	47
Spiral ganglion cell count	0.40836	.0006	47	0.46323	.0010	47	0.50663	.0030	47
% Normal spiral ganglion cell count (age-matched)	0.42743	.0027	47	0.41587	.0036	47	0.45259	.0015	47
% Remaining hair cells	0.21452	.1523	46	0.21452	.1523	46	0.21964	.1425	46
% Remaining pillar cells	0.21390	.1535	46	0.21390	.1535	46	0.23159	.1215	46
Maximum diameter of vestibular nerve	0.73803	.0001	47	1.00000	.0	47			

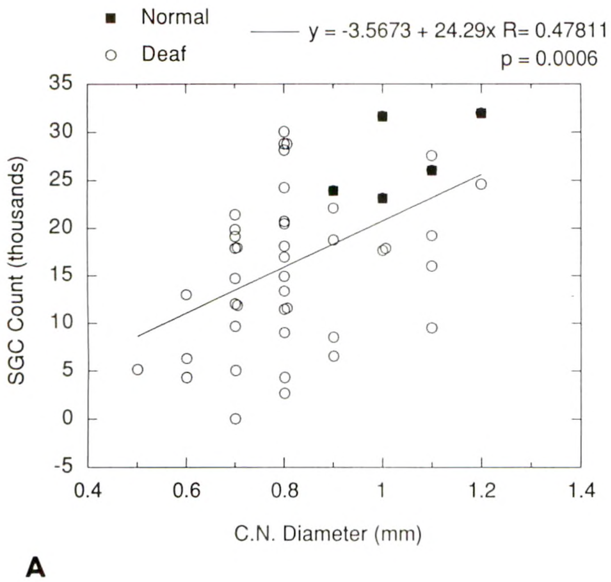
the temporal bone (left versus right) or the sex of the patient. In addition, there was no significant correlation with the age at death, the duration of hearing loss, the duration of deafness, the percent of remaining hair cells, or the percent of remaining pillar cells. However, the maximum diameters of the cochlear, vestibular, and eighth cranial nerves were strongly correlated with the spiral ganglion cell count ($p = .0006$, $p = .001$, and $p = .0003$, respectively) and the percent of normal age-matched spiral ganglion cell count ($p = .0027$, $p = .0036$, and $p = .0015$, respectively). The maximum diameter of the cochlear nerve was strongly correlated with the maximum diameter of the vestibular nerve ($p = .0001$). The scatterplots of spiral ganglion cell count versus diameters of the cochlear, vestibular, and eighth cranial nerves and regression lines are shown in Fig 1, and a histogram of spiral ganglion cell count by cochlear nerve diameter is shown in Fig 2.

DISCUSSION

Correlation of Nerve Diameter and Spiral Ganglion Cell Count. It is clear from the data that the maximum diameters of the cochlear, vestibular, and eighth cranial nerves are positively correlated with the remaining spiral ganglion cell count, and that the diameter of each of these nerves is smaller in deaf subjects than in normal controls. This implies that precise measurements of the maximum diameter of each of these nerves on preoperative imaging studies such as magnetic resonance imaging could be used as a predictor of the remaining spiral ganglion cell count and perhaps, in turn, as a means of prognostication of success of implantation.

However, the overlap in ranges of diameters in deaf and hearing ears and the lack of thorough understanding of the patterns of degeneration of the auditory nerve militate against the usefulness of this theoretically possible tool. As is apparent from Table 2 and Fig 1, there is considerable overlap in range of the maximum diameters of the nerves in deaf and normal-hearing individuals. Thus, the maximum diameters of the cochlear and eighth cranial nerves in deaf and normal individuals were the same (1.2 and 2.1 mm, respectively). In addition, although significantly different, the mean diameters for deaf and normal-hearing ears differ by only 0.23 mm for the cochlear nerve, 0.22 mm for the vestibular nerve, and 0.45 mm for the eighth cranial nerve. It is questionable whether this degree of precision is achievable, given the resolution of current imaging techniques.

Patterns of Degeneration of Human Cochlear Nerve. The pattern of degeneration of the auditory nerve remains controversial. In a recent series of papers, Spoendlin and Schrott[16-18] have demonstrated that in normal and pathologic human specimens, the number of spiral ganglion cells is approximately equivalent to the number of axons within the internal auditory canal and to the number of dendrites counted in the osseous spiral lamina. This corroborated earlier work in animal models[19] in which it was demonstrated that retrograde degeneration of the first-order auditory neuron occurs when either the central or peripheral process has been damaged and that in general, there is good correlation between counts of dendrites as measured in the osseous spiral lamina



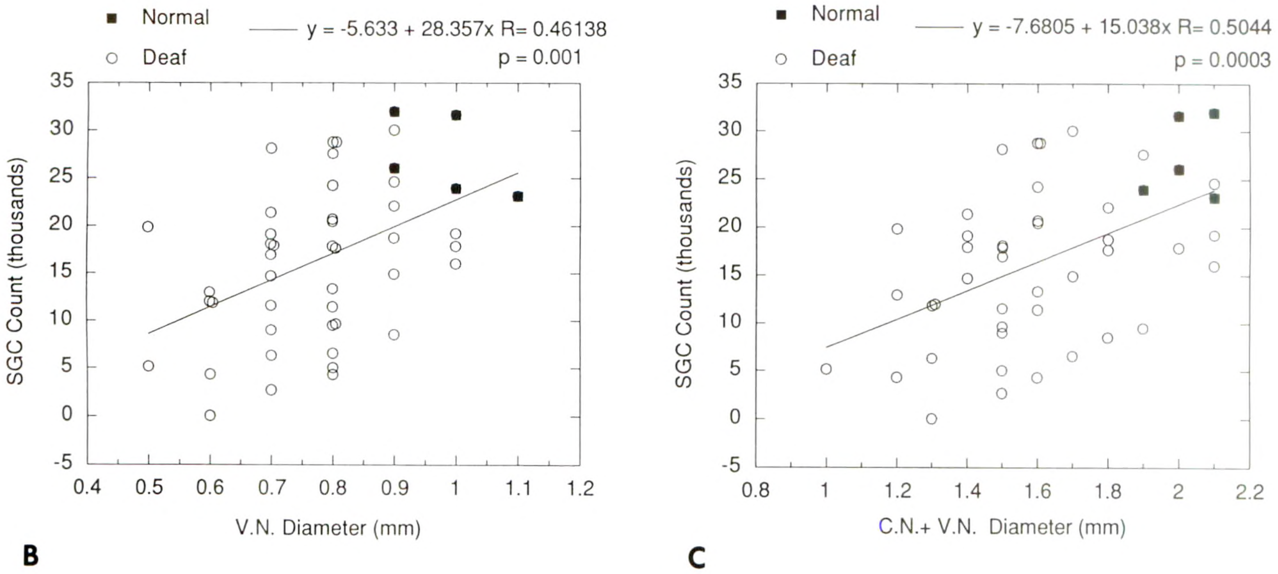


Fig 1. Scatterplots. (Note: Where data points overlapped, small increments were added to nerve diameters to separate data for purposes of Figure.) A) Of measured maximum diameters of cochlear nerve (C.N.) and spiral ganglion cell (SGC) count. Regression equation can be used to estimate SGC count as follows: y(SGC count) = −3,567 + 24,290 x maximum diameter of C.N. in millimeters. B) Of maximum diameters of vestibular nerve (V.N.) and SGC count. C) Of maximum diameters of eighth nerve (C.N + V.N.) and SGC count. Regression equation can be used to estimate SGC count, if eighth nerve diameter is known, as follows: y(SGC count) = −7,681 + 15,038 x maximum diameter of C.N. and maximum diameter of V.N. in millimeters.

and the number of spiral ganglion cells.

However, several investigators have demonstrated that in the human the number of axons as measured in the internal auditory canal may far exceed the number of dendrites as measured in the osseous spiral lamina. For example, Felix et al[20] found that there were always fewer dendrites than axons in human cases of sensorineural hearing loss, with differences up to 55%. In addition, the lower the number of dendrites, the greater the difference between axon and dendrite counts; this finding suggests that axons degenerate at a much slower rate than dendrites. In a semiquantitative study, Suzuka and Schuknecht[21] found that the loss of dendritic fibers was consistently greater than the loss of spiral ganglion cells in humans, and that following cochlear injuries, the soma may survive for many years without its dendritic process. This was substantiated in a study using transmission electron microscopy[22] of one case of long-standing profound deafness in which remaining spiral ganglion cells possessed no dendritic fibers but the axons were intact.

In seven surgical specimens of auditory nerves from humans undergoing translabyrinthine nerve sections, Ylikoski et al[23] reported that the nerve fiber population in these deaf individuals was near normal. However, this study was based on a sampling technique in which actual measurements were of the remaining axon density and the total count of axons was extrapolated. In a subsequent study,[24] "intact" cochlear nerves were reported in five deaf humans with severe degeneration of the spiral ganglion and cochlea as evaluated by light microscopy; this finding implied that auditory neurons may survive, at least for a time, after degeneration of the cochlea and spiral ganglion cells. However, the technique used to evaluate the integrity of the auditory nerve was semiquantitative.

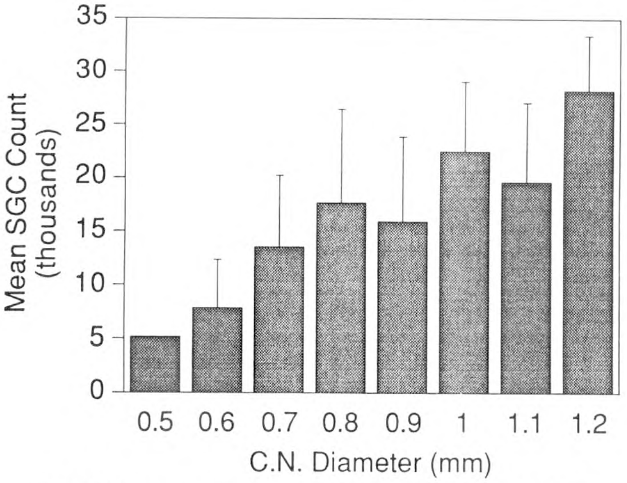


Fig 2. Histogram of mean and standard deviation of spiral ganglion (SGC) cell count by maximum diameter of cochlear nerve (C.N.) in millimeters.

The factors responsible for initiation of degeneration of spiral ganglion cells and their processes remain controversial. Putative causes for retrograde degeneration include loss of inner hair cells,[25] loss of supporting pillar and Deiters' cells,[26] and damage to the dendritic fibers within the osseous spiral lamina.[19,27,28] However, in the present study there was a lack of correlation between the diameter of the cochlear nerve and the percent remaining hair cells or percent remaining pillar cells (Table 3) that underscores our poor understanding of the factors that determine initiation of degeneration of the human auditory neuron.

Thus, it appears that there is not yet a consensus on the correlation between the number of auditory nerve fibers as measured in the internal auditory canal and the remaining spiral ganglion cell count and remaining dendritic fiber count. Although the time course of retrograde degeneration of cochlear axons in animals may not exceed 12 months,[27-29] the time course in humans may be much longer,[21,24] and hence may help to explain these apparently disparate findings.

If we assume that the number of axons as measured in the internal auditory canal will eventually come into parity with the number of spiral ganglion cells, it does not necessarily follow that this will result in a decrease in the diameter of the auditory nerve as measured by preoperative imaging techniques. There is a paucity of information concerning the correlation between auditory nerve diameter and the number of nerve fibers contained therein. In a quantitative study, Fujii et al[30] evaluated the cross-sectional morphology of the auditory and vestibular nerves in 12 human specimens. They found that the number of nerve fibers of both the auditory and the vestibular trunks failed to decrease with age. However, the diameter of the auditory nerve fibers did appear to decrease with advancing age. Felix and Hoffmann,[31] in a study of surgical specimens of cochlear nerves of humans who had suffered congenital or acquired deafness, demonstrated a wide variability of nerve fiber count and a considerable variability in interneuronal fibrosis and gliosis, which would be impossible to distinguish from nerve fiber by radiographic techniques. L. I. Terr and G. A. Sfogliano (personal communication, 1991) performed cross-sectional measurements of the auditory nerve in normal and deaf humans. They found that both the individual nerve fibers and the auditory nerve trunk itself were thinner in deaf individuals than in those with normal hearing. Thus, in the deaf group the mean cross-sectional area of the cochlear nerve trunk was 1.1 mm^2, whereas in normal-hearing individuals the area was 1.9 mm^2. Unfortunately, no correlation with residual spiral ganglion cell count was possible in this study. Additionally, these investigators suggested that the density of the nerve fibers within the auditory nerve trunk was reduced, but these results were not quantified.

Correlation Between Diameters of Cochlear and Vestibular Nerves. The significant correlation between the diameters of the cochlear and vestibular nerves (Table 3) was a surprising finding. This may imply that diseases that affect the cochlea tend also to involve the vestibular apparatus, a hypothesis supported by the positive correlation between counts of remaining Scarpa's ganglion cells and spiral ganglion cells[32] and the frequent coincidence of hypofunction on caloric tests in ears with markedly decreased spiral ganglion cell counts.[33]

In summary, by histologic measurements there is a significant positive correlation between the remaining spiral ganglion cell counts and the diameters of the cochlear, vestibular, and cochleovestibular nerves. The significant scatter of diameters may be due to delay in degeneration of nerve fibers or variation in interneuronal gliosis. Nevertheless, attempts to measure these nerves radiographically in cochlear implant candidates seem warranted in an effort to predict remaining spiral ganglion cell counts and perhaps to prognosticate success in speech perception. However, the wide variability in diameters of the eighth nerve in both deaf and hearing subjects militates against this theoretic usefulness.

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Ann Otol Rhinol Laryngol 101:1992

INFLUENCE OF GENERAL ANESTHESIA ON TRANSIENTLY EVOKED OTOACOUSTIC EMISSIONS IN HUMANS

ROLF HAUSER, MD
RUDOLF PROBST, MD
FRANCES P. HARRIS, PHD
FRANZ FREI, MD

BASEL, SWITZERLAND

The influence of general anesthesia (GA) on transiently evoked otoacoustic emissions (TEOAEs) was studied in 19 normally hearing women undergoing surgery. Emissions were measured on the day before the operation, after premedication but before the beginning of the operation, and during and after the operation. There were no significant differences in TEOAE amplitude or in reproducibility between results obtained the day before the operation and after premedication. Ten patients received nitrous oxide (N2O) during GA (N2O group), and 9 patients did not (non-N2O group). The amplitude of TEOAEs was reduced during GA in 9 of 10 patients in the N2O group and in 7 of 9 patients in the non-N2O group. However, the average decrease of amplitude after the first 10 minutes was greater in the N2O group (4 ± 3.4 dB) than in the non-N2O group (0.18 ± 1.4 dB). The corresponding mean reproducibility of the response decreased in 9 of 10 patients of the N2O group (29% ± 24%) and was nearly unchanged in the non-N2O group (2.3% ± 7.2%). The time course of the amplitude reduction was similar in both groups. The smallest amplitudes were reached on an average by 19.3 ± 11.4 minutes in the N2O group and by 17 ± 13.6 minutes in the non-N2O group. Preoperative and postoperative TEOAEs were comparable in level and reproducibility. Differential frequency effects imply a middle ear effect for the greater reduction of TEOAE amplitudes in the N2O group due to gas diffusion into the middle ear. The decreases in the amplitudes of TEOAEs in patients not receiving N2O indicate the presence of additional factors affecting the response during GA.

KEY WORDS — anesthesia, humans, normal ears, otoacoustic emissions.

INTRODUCTION

The influence of general anesthesia (GA) on transiently evoked otoacoustic emissions (TEOAEs) is of interest for several reasons. The measurement of TEOAEs is used increasingly as an objective hearing test,[1-7] and children may be tested under sedation or GA. The changes of TEOAEs under GA have to be known for such measurements. In addition, GA may exert an effect on the efferent portion of the cochlear innervation. Experimental results have suggested that this system may modulate TEOAEs in humans.[8-10] Drugs used for GA often act on neurotransmitters or neuromodulators, some of which have been shown to be present in the cochlea.[11-18] For example, benzodiazepines exhibit a close functional relationship to γ-aminobutyric acid (GABA) receptors[19,20] and act as coreceptors increasing the GABA-induced chloride ion influx into the cell. Atropine blocks acetylcholinergic mechanisms, and fentanyl citrate influences opioid receptors. These drugs are widely used during anesthesia.

An additional reason for studying TEOAEs during GA is the relative difficulty in recording TEOAEs in most laboratory animals, in contrast to other types of emissions. General anesthesia may be a factor contributing to this finding, because animals are generally tested under GA.[21-29] However, the enormous pharmacologic and physiologic complexity of GA and the fact that experimental manipulations cannot be carried out in humans limited the goal of this study to the evaluation of gross influences of GA on TEOAEs.

MATERIAL AND METHODS

Subjects. The subjects were 20 women, 18 to 52 years of age (mean 27.8 years), who underwent a gynecological surgical procedure under GA. They participated in the study after informed consent was obtained. All had normal middle ear status as measured by otoscopy and immitance procedures. Pure tone air conduction thresholds, obtained by standard audiometric methods, were ≤10 dB hearing level bilaterally at octave frequencies between 250 and 8,000 Hz.

Procedure. On the day before the surgical procedure, pure tone audiometry and immitance testing were performed. Click-evoked otoacoustic emissions (OAEs) were measured three times ("preoperative recording"). All measurements were performed with the patient in a recumbent position.

On the day of surgery, 30 to 60 minutes before the

From the Departments of Otorhinolaryngology (Hauser, Probst, Harris) and Anesthesiology (Frei), University of Basel, Basel, Switzerland.
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REPRINTS — Rolf Hauser, MD, Dept of Otorhinolaryngology, University of Basel, Kantonsspital, CH-4031, Basel, Switzerland.

TABLE 1. ECHO LEVEL AND REPRODUCIBILITY OF TEOAEs ON DAY BEFORE SURGERY, UNDER ANESTHESIA PREMEDICATION, AND AFTER ANESTHESIA (N = 19)

	Mean Echo Level ± 1 SD (dB SPL)	*Mean Reproducibility ± 1 SD (%)*
Preoperative		
Measurement 1	12.5 ± 3.1	87.5 ± 12.9
Measurement 2	12.8 ± 3.8	86.6 ± 15.8
Measurement 3	13.3 ± 3.5	92.5 ± 14.2
Premedication		
Measurement 1	12.5 ± 3.2	83.6 ± 11.1
Measurement 2	13.0 ± 2.9	85.1 ± 9.1
Measurement 3	13.5 ± 3.4	89.5 ± 10.5
Postoperative		
Measurement 1	11.8 ± 3.6	84.2 ± 8.9
Measurement 2	12.3 ± 3.8	84.5 ± 11.0
Measurement 3	12.5 ± 3.2	86.4 ± 9.5

TEOAEs — transiently evoked otoacoustic emissions, SPL — sound pressure level.

induction of GA and after premedication with atropine 0.01 mg/kg and/or midazolam hydrochloride 0.05 to 0.1 mg/kg, the measuring probe was positioned securely in one of the subject's ear canals. The ear selected to be tested was varied for consecutively examined patients and was kept unchanged during the entire surgical and anesthesiologic procedure. Immediately after placement of the probe, TEOAEs were recorded three times ("premedication recording").

During the GA, TEOAEs were recorded about every 2 minutes. Thirty minutes after termination of GA, TEOAEs were again recorded three times ("postoperative recording"). Typically, anesthesia was induced by methohexital together with midazolam or propofol, fentanyl citrate, and the muscle relaxant atracurium besylate. After endotracheal intubation, 10 patients received nitrous oxide (N2O) during GA (N2O group), and 10 patients received enflurane without any use of N2O. One patient not receiving N2O had to be excluded from analysis because the probe was loosened during GA.

Measurement of TEOAEs. An ILO88 otodynamics analyzer in combination with a portable computer (Pyramid Computers, Freiburg, Germany) was used to stimulate and record the emissions. Stimuli were 80-microsecond rectangular pulses that were presented at a 20-millisecond rate in a stimulus array canceling linearly increasing portions of the responses. Three stimuli of equal size and polarity were followed by a fourth stimulus three times greater in amplitude and of inverted polarity. This format is used to extract the low-level, nonlinear cochlear emission from the higher-level linear stimulus and response components. It is a software option of the ILO88 and has been described fully elsewhere.[30] The stimulus level was adjusted until the microphone detected a peak stimulus level of 75 to 80 dB sound pressure level (SPL). This SPL assured the performance of measurements in saturation of the TEOAEs, as recommended for clinical purposes.[7] It was kept constant (±1 dB) during all measurements within a single subject. This condition compensated for the variability introduced by probe placement and for individual differences in impedance characteristics.

Acoustic measurements performed in operating rooms are difficult to perform because of the high level of environmental noise. Therefore, precautions were taken to avoid the influence of noise as much as possible. Throughout testing, probe stability and noise levels were monitored by the probe microphone and the ILO88 software options. The surgeons and the other staff were instructed to reduce noise as far as possible during the operation. In an attempt to reduce environmental noise further, circumaural ear protectors were fitted to the patient, and the artifact rejection algorithms were adjusted to a maximum between 43 and 48 dB SPL. Under this limit, the mean noise during accepted data was within a reasonable range below 40 dB. The resulting percentage of measurements rejected by the artifact rejection algorithm was equal to or smaller than 50% for all single measurements. Responses were stored after completion of 260 averages for a single measurement.

Data Analysis. Three parameters were selected to assess the variability across the longitudinal measurements. Amplitude was expressed as "echo level," which is a numeric value referring to the power of the response waveform and converted to decibels SPL by using the calibration values of the microphone.[30,31] Second, reproducibility was expressed as a cross correlation of two interleaved recorded waveforms. Third, each response waveform was transformed into its power spectrum by means of a fast Fourier transformation (FFT). The variability of the frequency spectrum amplitude was evaluated within 200-Hz-wide spectral bands from 0.7 to 5.8 kHz. Data analyses included computations of unpaired t tests between arithmetic group means.

RESULTS

No significant changes of amplitude or reproducibility were noted between the TEOAE measurements the day before surgery, under premedication with atropine and/or midazolam, and after the GA. The corresponding values are given in Table 1.

The pattern of TEOAE changes during GA was more uniform in patients receiving N2O. Nine of 10

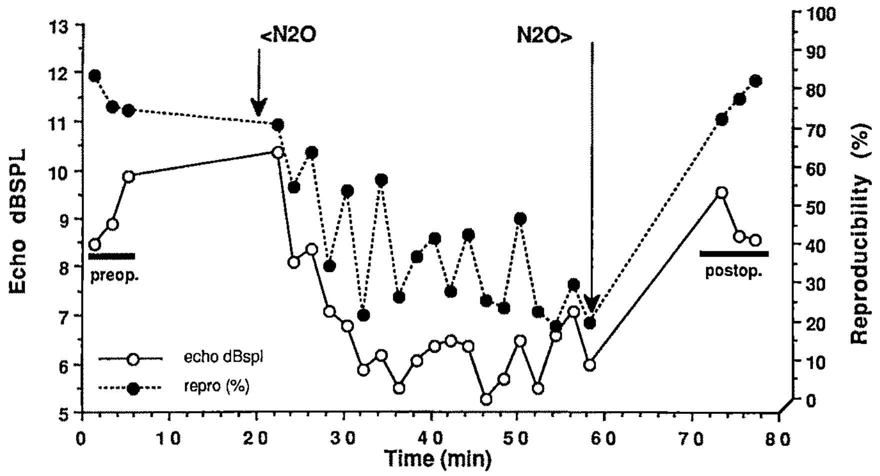

Fig 1. Typical behavior of amplitude expressed as "echo level" (white circles, left axis) and reproducibility (black circles, right axis) of one transiently evoked otoacoustic emission measured during nitrous oxide (N2O) anesthesia. Both values decrease after introduction of N2O and increase after application of N2O has been finished.

patients showed marked reductions of amplitude and reproducibility. A typical individual example is shown in Fig 1. The overall measuring conditions in this example were relatively stable, with a fixed noise rejection level of 45.3 dB, a mean noise of 35.7 ± 1.1 dB SPL during accepted data, and a mean percentage of 81% ± 15% of accepted measurements. A steep decrease of the amplitude from about 10.3 down to about 6.8 dB SPL and reproducibility from 72% to about 35% was observed within the first 10 minutes after the beginning of N2O application. Analysis of the mean power spectra revealed that variability during N2O anesthesia was highest in the frequency range of 1 to 2 kHz, as shown in Fig 2A.

A smaller reduction of TEOAE amplitude was recorded in the non-N2O group than in the N2O group. A decrease of amplitude could be documented in seven of nine patients. Reproducibility was nearly unchanged. An individual example is given in Fig 3. The measuring conditions for this example were relatively good and were comparable to those described for the example in Fig 1 when extraneous noise levels are considered. The fixed noise rejection level was 45.3 dB, the mean noise during accepted data 35.4 ± 1.0 dB SPL, and the mean percentage of accepted measurements 74% ± 18%. While a decrease of the emission amplitude from around 13 to 9.5 dB SPL was noted, reproducibility was not changed systematically and remained around 80%. Under the non-N2O anesthesia condition, there were small changes in the frequency range 1 to 2 kHz (Fig 2B).

Table 2 summarizes the mean changes of TEOAE amplitude and reproducibility after the first 10 minutes of anesthesia together with the time until the minimum of the emission amplitude was measured. The time course of the amplitude reduction was similar in both groups. The minima of the reproducibility of the non-N2O group were all above 60%, whereas 9 of 10 patients of the N2O group showed minima below 60%.

DISCUSSION

Systematic examinations of the influence of GA on OAEs were performed by Probst and Beck[32] for spontaneous otoacoustic emissions (SOAEs). They

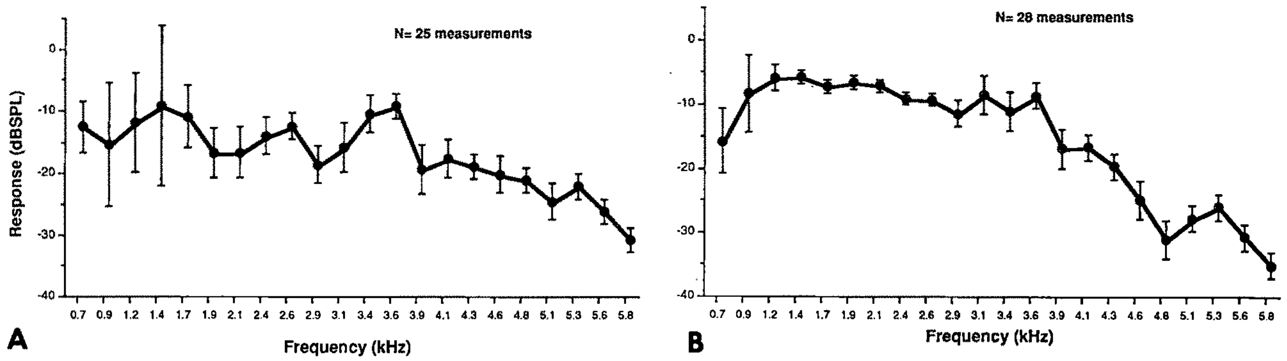

Fig 2. Variability of power spectra levels within frequency bands of 200 and 300 Hz. Line connects mean levels of all measurements of A) subjects who received nitrous oxide anesthesia and B) those who did not. Vertical bars — 1 SD. A) Variability during nitrous oxide anesthesia is marked in frequency range from 1 to 2 kHz, which is primarily determined by middle ear. Higher frequencies are less influenced by positive middle ear pressure. B) During measurements without application of nitrous oxide, there were extremely small changes in lower frequency region between 1 and 2 kHz, whereas variability was higher in upper frequency range.

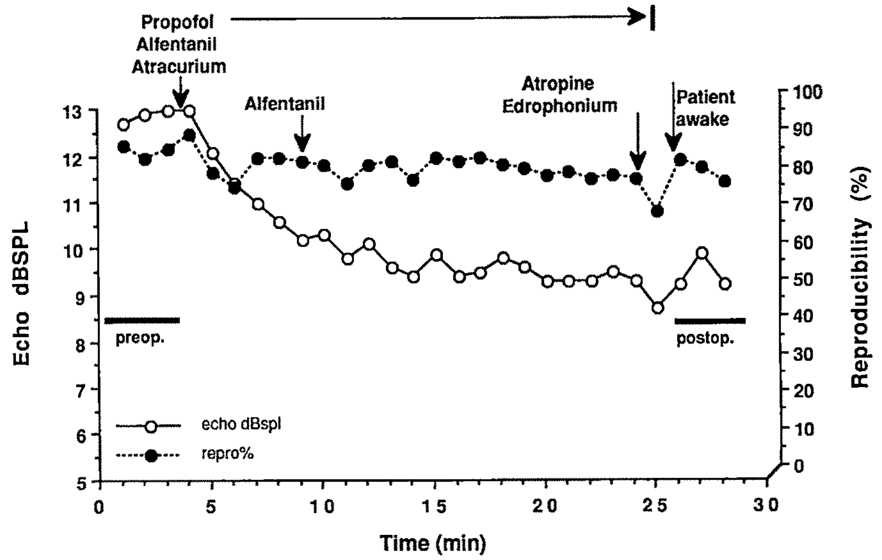

Fig 3. Behavior of one transiently evoked otoacoustic emission during anesthesia without use of nitrous oxide (N2O). Reproducibility (black circles, right axis) stays nearly constant, whereas response amplitude (white circles, left axis) decreases and does not increase again until after cessation of anesthesia.

examined the behavior of 13 SOAEs in 10 subjects during GA. Generally, SOAEs were not abolished during anesthesia. Systematic patterns of changes could not be recognized. A minority of the examined SOAEs showed negatively correlated changes of amplitudes and frequencies indicating a possible middle ear influence with the use of N2O and muscle relaxants. All SOAEs remained measurable during the entire time course of the GA. The study of SOAEs during anesthesia is more difficult than the measurement of TEOAEs with the advanced cochlear echo technique described by Bray and Kemp.[30] This technique includes several artifact rejection procedures and thereby increases the signal-noise ratio. Moreover, the intrinsic variability of SOAE amplitude during relatively short time courses could influence the outcome of such a study.[33-35]

In this study, click-evoked OAEs remained generally detectable during anesthesia. Extraneous noise levels could be controlled, within reasonable limits, when circumaural ear protectors were fitted and the staff was instructed to avoid unnecessary noise. However, amplitudes and reproducibilities of the emissions were greatly reduced during the use of N2O as a narcotic gas. In these cases, the presence of TEOAEs could not always be confirmed reliably. Therefore, N2O should be avoided when TEOAEs are measured during GA. The decrease of TEOAE amplitude and reproducibility during N2O inhalation is most likely induced by changes in the transfer function of the middle ear. Nitrous oxide is known to diffuse through mucous membranes, and gas pressure can build up within the middle ear.[36-39] Such pressure changes can be exchanged only passively during GA because of paralysis of the eustachian tube opening by muscle relaxants. A reduction of OAE amplitudes by changes in middle ear pressure has been demonstrated by several authors.[7,33,40-42] This reduction affected mainly the 1- to 2-kHz region without influencing the higher-frequency region. The same pattern of frequency-specific amplitude reduction was found during GA with N2O, but not without N2O. This finding argues strongly for a middle ear influence.

A small and systematic reduction in amplitude, but not in reproducibility, was noted also in subjects not anesthetized with N2O. The similar time course of this amplitude reduction in the N2O group and in the non-N2O group is an indication that the reduction is probably a result of the GA itself. However, no systematic influences of specific drugs or of the depth of GA could be detected. An effect of the efferent system cannot be ruled out, nor can it be demonstrated by this study. It is possible that such influences would be more pronounced when TEOAEs are measured with a lower stimulus intensity not driving the emissions into saturation.

Premedication did not influence TEOAEs significantly (Table 1). It can be concluded that the usual

TABLE 2. CHANGES OF MEAN TEOAE AMPLITUDES AND MEAN TIME COURSE OF TEOAE AMPLITUDE CHANGES DURING ANESTHESIA

	Change in Amplitude (dB SPL)		*Mean ± SD Time to Amplitude Minimum (min)*	*Change in Reproducibility (%)*	
	Mean ± SD	*Range*		*Mean ± SD*	*Range*
N2O group (N = 10)	−4 ± 3.4	−10.2 to 2	−19.3 ± 11.4	−29 ± 24	−58 to 7
Non-N2O group (N = 9)	−0.18 ± 1.4	−3 to 1.4	−17 ± 13.2	−2 ± 7	−4 to 19

TEOAE — transiently evoked otoacoustic emission, SPL — sound pressure level, N2O — nitrous oxide.

dosages of benzodiazepines (midazolam) and atropine do not change TEOAEs (saturation). Evidence that atropine can influence TEOAEs in humans has been reported by Quaranta and Salonna[43] in a study of 10 normal hearing ears in which postatropine results exhibited a statistically significant reduction of ≥10 dB of the TEOAE detection threshold in seven subjects, and in two subjects a reduction of the TEOAE saturation thresholds was observed. Our study could not reproduce these results, possibly because the measurements were performed in saturation of TEOAEs, whereas Quaranta and Salonna[43] measured the TEOAEs using SPLs not driving the TEOAEs into saturation. In conclusion, our results indicate that besides some unexplained effects of GA on TEOAEs, stable recording of TEOAEs should be possible under sedation with the drugs reported in this study, at least at relatively high stimulation levels of about 75 to 80 dB SPL and when N2O as a narcotic gas is avoided.

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FOURTH INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON INNER EAR MEDICINE AND SURGERY

The Fourth International Symposium and Workshops on Inner Ear Medicine and Surgery will be held July 17-24, 1994, in Snowmass-Aspen, Colorado. For more information, please contact I. Kaufman Arenberg, MD, Executive Director and Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone 303-788-4320 or 303-850-9545; fax 303-788-4234.

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1993 CONFERENCE ON IMPLANTABLE AUDITORY PROSTHESES

The 1993 Conference on Implantable Auditory Prostheses will be held July 11-15, 1993, on the campus of Bryant College in Smithfield, Rhode Island. This is the sixth in a series of biennial research conferences originating with the 1983 Gordon Conference. The meeting will provide a forum for close interaction among scientists in all disciplines relating to the field of cochlear implants. For further information, contact Chris van den Honert, Division of Otolaryngology–Head & Neck Surgery, Box 3550, Duke University Medical Center, Durham, NC 27710; Telephone: (919) 684-6099, E-Mail: chx@dukehrl.mc.duke.edu.

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ANTIBODIES AGAINST A 30 KILODALTON COCHLEAR PROTEIN AND TYPE II AND IX COLLAGENS IN THE SERUM OF PATIENTS WITH INNER EAR DISEASES

THOMAS JOLIAT, MD
BLOOMFIELD HILLS, MICHIGAN
JEROME SEYER, PHD
MEMPHIS, TENNESSEE
JOEL BERNSTEIN, MD
BUFFALO, NEW YORK
MARC KRUG, PHD
MEMPHIS, TENNESSEE
X. J. YE, MD
MEMPHIS, TENNESSEE
J. S. CHO, MD
SEOUL, SOUTH KOREA
T. FUJIYOSHI, MD, PHD
MEMPHIS, TENNESSEE
T. J. YOO, MD, PHD
MEMPHIS, TENNESSEE

Collagen molecules are major extracellular matrix proteins involved in the development and support of delicate auditory sensory organs. Type II collagen is widely distributed within inner ear tissues, while type IX is found only within the labyrinthine membrane and dense fibers of the tectorial membrane. Antibody specific for type II collagen has been shown to be elevated in some patients with hearing loss due to several presumably autoimmune illnesses (including Meniere's disease, otosclerosis, chronic progressive sensorineural hearing loss, and relapsing polychondritis). Purified human type II and IX collagens and an extract of human cochlear tissue were subjected to isolation by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to nitrocellulose. The sera of 21 patients with inner ear disease were examined for the presence of anticollagen and anticochlear antibodies; the sera were used to probe Western blots of purified human collagens II, IX, and XI, and cochlear protein extract with peroxidase-conjugated goat anti human polyvalent immunoglobulin as the second antibody. Anti–type II collagen antibodies were seen in 12 of 21 (57%) patients, while 13 of 21 (62%) had anti–type IX antibodies detectable by Western blot. A previously unreported 30 kd (probably noncollagen) protein was found by SDS-PAGE of human cochlear tissue extracts, with 3 patients, all with Meniere's disease, having antibody activity to this protein detected by Western blot. Anti–type II and anti–type IX antibodies were found in a high percentage of patients with Meniere's disease, otosclerosis, and strial atrophy. Six patients (29%), and all control patients, had no detectable antibodies to these proteins by our assay.

KEY WORDS — antibody, cochlear protein, collagen, Western blot.

INTRODUCTION

Hearing loss is common. In many cases auditory dysfunction can be traced to a conductive defect that occurs with perforated tympanic membranes, otitis media, cholesteatoma, discontinuity of ossicles, and so on. Noncochlear sensorineural hearing losses can be due to tumors, such as acoustic neuroma, or central nervous system lesions. While inner ear sensorineural hearing loss can be due to processes whose cause is clearly understood, such as noise or drug-induced cochlear damage or presbycusis, there exist several forms of cochlear sensorineural hearing loss of which the cause and full pathogenesis have defied clear definition.

On the basis of animal and human studies, an underlying immune dysfunction is now thought to contribute in whole or in part to the pathogenesis of several of these previously ill-defined diseases, including sudden hearing loss,[1,2] Meniere's disease,[3,4] chronic progressive sensorineural hearing loss (CPSNHL),[5-9] (also J. J. Shea and T. J. Yoo, unpublished observations, 1982), and otosclerosis.[10,11]

Animal studies have associated laboratory inoculation of cochlear components with the development of autoantibodies, cochlear lesions, and sensorineural hearing loss.[12-14] Furthermore, experimental induction of CPSNHL has been produced by immunization of animals with purified type II collagen, giving rise to specific anti–type II collagen antibodies and inner ear lesions histologically similar to those seen in CPSNHL and Meniere's disease.[8,9,15,16]

In this study, then, we attempted to define in human sera the presence and character of anticollagen and anticochlear antibodies. Human cochlear protein was extracted and separated via gel electrophoresis and analyzed for immunoreactivity along with human type II and IX collagens by Western blotting. Blots were probed with sera from 21 patients with various inner ear diseases.

MATERIALS AND METHODS

Patient Selection. Sera from 21 patients with vari-

From the Division of Allergy and Immunology, University of Tennessee, Memphis, Tennessee (Joliat, Seyer, Krug, Ye, Fujiyoshi, Yoo), the Department of Otolaryngology, State University of New York at Buffalo, Buffalo, New York (Bernstein), and the Department of Otolaryngology, Kyung-Hee University, Seoul, South Korea (Cho). Dr Joliat is currently in private practice in Bloomfield Hills, Michigan.

REPRINTS — T. J. Yoo, MD, PhD, University of Tennessee, Memphis, 956 Court Ave, Room H300, Memphis, TN 38163.

TABLE 1. PATIENT DIAGNOSES

Patient No.	*Diagnosis*
1	Meniere's disease
2	Meniere's disease
3	Idiopathic sensorineural hearing loss
4	Bell's palsy
5	Idiopathic sensorineural hearing loss
6	Cochlear contusion
7	Sudden deafness
8	Meniere's disease
9	Strial atrophy
10	Strial atrophy
11	Meniere's disease
12	Otosclerosis
13	Meniere's disease
14	Otosclerosis
15	Sudden deafness
16	Otosclerosis
17	Vestibular neuritis
18	Meniere's disease
19	Otosclerosis
20	Vestibular neuritis
21	Vestibular neuritis
22	(Control)
23	(Control)
24	(Control)
25	(Control)

ous inner ear diseases were supplied courtesy of Drs J. Bernstein and J. S. Cho. Patient diagnoses are presented in Table 1. Six patients had Meniere's disease, while 4 patients each had otosclerosis and sudden deafness or idiopathic sensorineural hearing loss. Two patients had strial atrophy (presbycusis) and 3 had vestibular neuritis. One patient had Bell's palsy and another a cochlear contusion. Four normal control subjects were included in this study.

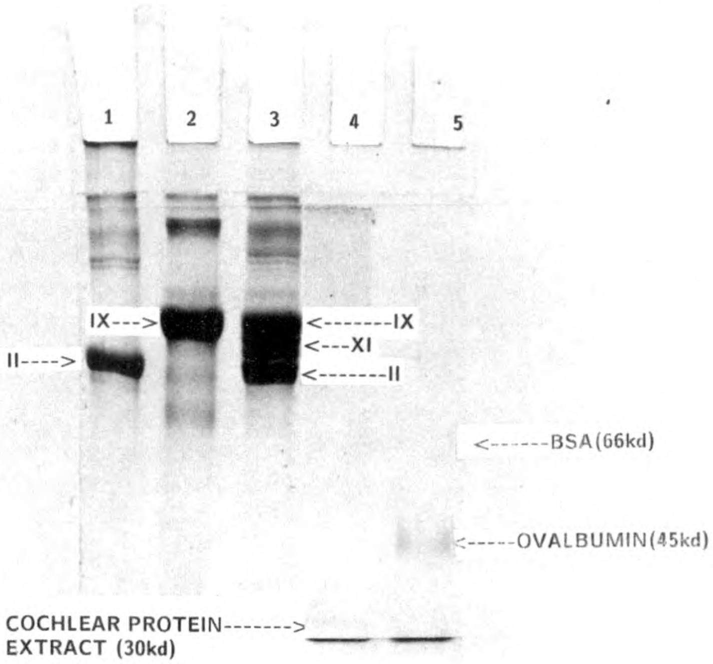
Preparation of Cochlear Tissue. Human cochlear tissues used in these experiments were obtained from living patients undergoing inner ear microsurgical dissection. Specimens were stored frozen in phosphate-buffered saline (courtesy Drs G. Gardner and D. Brackmann). The tissue was cleaned, teased apart, homogenized in several milliliters of distilled water, and vortexed. The resultant suspension was centrifuged at 7,000 rpm for 10 minutes and the supernatant was decanted and frozen. This procedure was repeated three times. The residues were then each suspended in 500 µL of a lysis buffer (0.5% NONIDET P-40 octylphenoxypolyethoxyethanol, 1 mmol/L iodoacetamide, 0.2% aprotinin, and 2 µg soybean trypsin inhibitor in 100 mL 0.05 mol/L Tris), vortexed, and centrifuged, and the supernatant was decanted. This procedure was repeated twice. The residues were then washed again three times with distilled water. Finally, the residues were resuspended in water and subjected to sonication (Branson Sonifier 450) for 10 minutes, vortexed, and centrifuged, and the supernatant was decanted and frozen. This procedure was repeated twice. All supernatants were combined, filtered (0.22-µm Millipore filter), and stored frozen. At no time were the samples subjected to proteolytic degradation. Finally, supernatants were lyophilized and desalted by Centricon filtration, and the protein extract was stored at −70°C.

Gel Electrophoresis. Electrophoresis was performed in a Mini-Protean (Bio-Rad) apparatus utilizing a 6% polyacrylamide sodium dodecyl sulfate (SDS) gel. After meticulous washing of electrophoresis plates the apparatus was assembled. Six percent SDS–polyacrylamide gel electrophoresis (PAGE) running gel (3.75 mL stock acrylamide [30% + 0.8% Bis], 10 mL high-performance liquid chromatography [HPLC]–grade water [H_2O], 4.7 mL 2x running gel, and 275 µL 10% 2x SDS, pH 8.3) was polymerized with 250 µL of 1% ammonium persulfate and 18.75 µL tetramethylethylenediamine and infused into the apparatus.

Water-saturated butanol was layered on top of the running gel to promote a smooth interface. Polymerization was allowed to occur and the butanol was removed. Then a 4% stacking gel (1.3 mL stock acrylamide, 5.4 mL HPLC-grade H_2O, 2.5 mL 2x stacking gel buffer [0.5 mol/L Tris, 0.4% SDS pH 6.8]) polymerized with 5 µL N, N, N′, N′-tetramethylethylenediamine and 75 µL ammonium persulfate was infused on top of the solidified running gel. A 10-well minigel "comb" was then inserted and the gel was allowed to polymerize.

Small amounts of purified, lyophilized human collagens type II and type IX, a mixture containing types II, IX, and XI,[17] and cochlear extract were each suspended in 50 µL HPLC-grade H_2O to which was added 50 µL of sample buffer (containing 2% SDS, 5% 2-mercaptoethanol, 10% glycerol, and 0.001% bromphenol blue in a 0.0625 mol/L Tris buffer; pH 6.8). The resulting solution was then heated 3 minutes at 100°C (Thermodyne Dri-Bath) and 5- to 15-µL aliquots were micropipetted into respective lanes of the minigel. To some of the initial minigels were added purified bovine serum albumin and ovalbumin as known–molecular weight standards.

The constructed minigel apparatus was placed in the Mini-Protean chamber filled with electrode buffer (14.4 g/L glycine, 3.03 g/L Tris, and 1.0 g/L SDS in distilled water; pH 8.8) and subjected to a 50-mA-per-gel current until the dye front was 1.5 cm above the bottom of the plates (generally about 2 hours). Separated proteins were then stained with Coomassie brilliant blue (R-250) and destained with 10% metha-



Six percent polyacrylamide–sodium dodecyl sulfate gel. Lane 1 — lyophilized human type II collagen (molecular weight [MW] 95 kd), lane 2 — type IX collagen (MW 100 kd), lane 3 — lyophilized mixture of human type II, IX, and XI collagens, lane 4 — extracted human cochlear protein (MW approximately 30 kd), lane 5 — bovine serum albumin (BSA; MW 66 kd) and ovalbumin (45 kd). See text for details.

nol and 7% acetic acid in distilled H_2O or transferred immediately to nitrocellulose membranes.

Transfer of Proteins to Nitrocellulose Membranes. Electrophoresed protein gels were placed on wetted filter paper and each was overlaid with a closely fitting precut and prewetted sheet of nitrocellulose (Schleicher & Schuell Co, Keene, NH). Another piece of prewetted filter paper was placed on the nitrocellulose and the air bubbles were removed. This was sandwiched into the transblot support apparatus (Bio-Rad) and the support was placed in the electroblotting chamber (Bio-Rad Trans Blot Cell). The tank was filled with fresh transblot buffer (300 mL 0.1 mol/L 3-(cyclohexylamino)-1-propane sulfonic acid, 300 mL isopropyl alcohol, 2,400 mL HPLC-grade H_2O; pH was adjusted to 11.0 with 1N sodium hydroxide) and subjected to 450 mA current (limit 600 mA) for 6 hours, during which active cooling of the buffer occurred. After transfer, several membranes were then stained with Amido black to ensure successful transfer, while others were placed in sealed plastic bags containing washing buffer (6.06 g/L Tris, 8.77 g/L sodium chloride, and distilled H_2O to 11, adjusted with 12N hydrochloric acid to pH 7.5) with 0.05% Tween 20, and kept refrigerated until used for Western blot analysis.

Western Blotting. Each blotted membrane was washed with washing buffer. Nonspecific antibody binding was blocked by adding 2 to 3 mL of 100% goat serum and rocking at room temperature for 1 hour. The washed transblot paper was then sealed in a plastic bag with 10 mL of washing buffer containing 25% normal goal serum and patient serum in a 1:50 dilution. The paper was incubated overnight with the first antibody at 4°C on a rocker.

The paper was then washed four times, each with 30 to 40 mL of washing buffer, for 15 minutes on a rocker. The paper was then reacted with a peroxidase-conjugated goat anti human polyvalent immunoglobulin (Sigma Chemical Co, St Louis, Mo) for 2 hours at room temperature (1:1,000 goat anti-immunoglobulin antibody) in washing buffer containing 1% normal goat serum.[18] The washed paper was then stained in sealed bags with substrate (containing 50 mL washing buffer, 30 mg 4-chloro-1-naphthol in 10 mL methanol, and 30 μL 30% hydrogen peroxide) for 1 hour at room temperature.

RESULTS

The SDS-PAGE of the various collagens, cochlear extract, and known–molecular weight standards yielded the patterns illustrated in the Figure. Lane 1, aliquoted with 10 μL of type II collagen, discloses a sharply defined band, corresponding to the α1 (II) chain of type II collagen at approximately 95 kd. Similarly, lane 2, with 10 μL of type IX collagen, displays a single band corresponding to the high–molecular weight (HMW) complex of type IX collagen at approximately 100 kd. Lane 3, containing a 10-μL aliquot of a lyophilized mixture of type II, IX, and XI collagens, displays five bands corresponding to the α1 (II) and HMW chains of type II and IX collagens, respectively, and three additional bands corresponding to the α1 (XI), α2 (XI), and α3 (XI)

TABLE 2. WESTERN BLOT RESULTS OF TYPE II AND IX COLLAGENS AND COCHLEAR PROTEIN PROBED WITH SERA FROM PATIENTS WITH VARIOUS INNER EAR DISEASES

Inner Ear Disease	*Pt No.*	*Type II*	*Type IX*	*Cochlear Protein*
Meniere's disease	1	++	++	+
	2	–	+	–
	8	++	–	+
	11	–	–	–
	13	+	++	+
	18	+	++	–
Otosclerosis	12	+	+	–
	14	+	++	–
	16	+	++	–
	19	–	–	–
Strial atrophy	9	++	++	–
	10	++	++	–
Idiopathic SNHL or sudden deafness	3	–	–	–
	5	–	–	–
	7	–	–	–
	15	+	–	–
Vestibular neuritis	17	–	++	–
	20	+	++	–
	21	–	+	–
Bell's palsy	4	–	–	–
Cochlear contusion	6	++	++	–
Controls	22	–	–	–
	23	–	–	–
	24	–	–	–
	25	–	–	–
Totals		12/21 (57%)	13/21 (62%)	3/21 (14%)

SNHL — sensorineural hearing loss, ++ indicates strong antibody binding on Western blot, + indicates moderate antibody binding on Western blot, – indicates no discernible binding on Western blot.

chains of type XI collagen. It can be seen that $\alpha3$ (XI) comigrates with $\alpha1$ (II), and $\alpha1$ (XI) migrates slightly faster than the HMW complex of type IX collagen. The position of $\alpha2$ (XI), clearly seen, is equidistant between $\alpha1$ (XI) and $\alpha3$ (XI).These patterns are in accordance with previously published results.[17] In some gels in lanes 2 and 3, a faint band was found at approximately 55 kd. This corresponds to a low–molecular weight (LMW) fragment of type IX collagen present under reducing conditions (data not shown). Lane 4 contains a 15-µL aliquot of cochlear protein extract. A faint band stained with Coomassie blue, running at approximately 30 kd, can be discerned. Finally, in lane 5 can be seen bands corresponding to bovine serum albumin (66 kd) and ovalbumin (45 kd), used as known–molecular weight standards.

Results of Western blotting procedures are presented in Table 2, which categorizes results according to disease diagnosis. Western blotting data from six patients with Meniere's disease are presented. Antibodies against type II collagen were detected in the sera of four patients (66%), while anti–type IX antibodies were found also in four patients (66%). Three patients (50%) had both anti–type II and anti–type IX antibodies detected in their sera, while one patient (patient 11) had no detectable antibody activity against these proteins. Three patients (50%) had positive Western blot results with the 30 kd extracted cochlear protein. Three of the four patients (75%) with otosclerosis had detectable antibody activity against both type II and type IX collagens. One patient failed to react to these proteins, and no patient had discernible activity against the 30 kd cochlear protein by our assay. Both patients with strial atrophy exhibited very strong activity against both type II and type IX collagens, but no detectable antibody activity against the extracted cochlear protein was seen. There were four patients with sudden or idiopathic sensorineural hearing loss. Only one patient (patient 15) demonstrated weak antibody activity against type II collagen. All patients failed to show detectable antibody activity against type IX collagen and the 30 kd cochlear protein. Three patients had the diagnosis of vestibular neuritis. One patient (patient 20) demonstrated weak antibody activity against type II collagen, while all three patients showed detectable antibody activity against type IX collagen. None of the three patients elicited any antibody activity against the cochlear protein. Table 2 also presents Western blot results from patient 4, with Bell's palsy, patient 6, with a history of a previous contusion to the head involving the inner ear structures, and four healthy control subjects. No patient had any discernible antibody activity against cochlear protein. Patient 6, solely, demonstrated activity against type II and IX collagens.

Overall, it can be seen that 12 of 21 (57%) of patients with various inner ear diseases had serum antibodies specific for type II collagen, while 13 of 21 (62%) had antibody activity specific for type IX collagen. Three of 21 (14%) patients had detectable antibody activity against the extracted 30 kd cochlear protein, with this antibody specificity found only in patients with Meniere's disease.

DISCUSSION

The etiopathogenetic mechanisms of several inner ear diseases associated with hearing loss, including idiopathic bilateral Meniere's disease, otosclerosis, and CPSNHL, have yet to be fully defined. The weight of recent evidence strongly implicates immunologic and/or chronic inflammatory processes as contributing to the pathogenesis of these illnesses.

It is hypothesized that some inciting event, perhaps a viral infection and/or its resultant inflammation, induces alteration, denaturation, substituted chemical modification (haptenization), or increased exposure of native and/or "sequestered" proteins.[12] Similarly, immune complexes, associated with certain rheumatic diseases, bacterial and viral infections, and tumor antigens, could be deposited within the stria vascularis (a structure similar to the renal glomerulus) and invoke a local inflammatory response that denatures or exposes native proteins.[19,20] Such proteins would then be taken up by local and recruited antigen-presenting cells (B cells and macrophages)[21-23] and transported to the endolymphatic sac,[24-26] where endosomally degraded peptides would be presented,[27,28] in the context of major histocompatibility complex (MHC) molecules,[29,30] to resident T lymphocytes. If at this point the patient was of a genetic constitution such that the peptide MHC was recognized as nonself (ie, tolerance did not exist), specific T cell clonal expansion, homing, and cytokine release would occur with the induction of an autoimmune response giving rise to specific (auto)antibody formation, complement cascade activation, inflammatory cell recruitment, mediator release, and, ultimately, tissue damage.

Immunologic tissue damage, if localized to the endolymphatic duct, would result in decreased endolymphatic fluid resorption and subsequent volume increase. This in turn would give rise to distortion and periodic rupture of the membranous labyrinth with contamination of perilymphatic fluid, causing the repeated episodes of vertigo and fluctuating hearing loss characteristic of Meniere's disease. Similarly, specific immunologic damage to cartilaginous components of the auditory ossicles and otic capsule would produce the otospongiotic lesions and clinical findings of otosclerosis. Finally, autoimmune-mediated damage to the connective tissue framework supporting the transducing hair cells would result in their collateral damage, with subsequent hearing loss.

Type II collagen, found only in avascular compartments (an immunologically "privileged" site),[31,32] exists within the subepithelial layer of the endolymphatic duct, as well as within the enchondral layer of the otic capsule, macular utricle and saccule, and ampullary crista.[16] Type IX collagen is less abundant and is located within the labyrinthine membranes, as well as within the dense fibers of the tectorial membrane.[33] These large, immunogenic, but "sequestered" proteins would serve as excellent targets of immune attack on inflammatory alteration or exposure.

Indeed, exogenous administration of purified type II collagen to susceptible laboratory animals (with subsequent uptake and degradation by circulating antigen-presenting cells to approximate the inciting events listed above) has produced a tissue damage model histologically similar to that seen in Meniere's disease and otosclerosis. Specifically, spiral ganglion degeneration, organ of Corti atrophy, spongification of the ossicles, disrupted vascular stria, extension of Reissner's membrane, surface epithelial atrophy, and an exuberant mononuclear cell infiltrate are seen.[9,16] Additionally, immunofluorescence studies disclose deposition of type II collagen–specific immunoglobulin G and complement along the endolymphatic duct surface epithelium.[16] These changes coincide in these animals with progressive hearing loss as measured by brain stem evoked potentials.[8,9] It has been further discovered that cyanogen bromide cleavage peptide 11 (CB-11) of type II collagen bears the epitope crucial for the induction of autoimmune inner ear disease in experimental animals. Administration of CB-11–specific monoclonal antibodies will produce ear lesions histologically similar to those seen in relapsing polychondritis.[34] Support for the role of type II antibodies in some inner ear diseases is further suggested by previous studies within this laboratory demonstrating significant (versus controls) elevations of type II–specific antibodies in the serum of patients with Meniere's disease and otosclerosis.[35]

The present studies extend these findings within the human system. We have found that a substantial overall percentage of patients with various inner ear diseases have autoantibodies specific for human type II (57%) or type IX (62%) collagen in their serum, detectable by a qualitative Western blot. Patients with Meniere's disease, otosclerosis, and strial atrophy (inner ear disease with a hypothesized immunopathogenetic contribution) were found to most frequently demonstrate anticollagen antibody activity in our Western blot assay, while patients with idiopathic or sudden hearing loss rarely did so. Further studies to determine the isotypes of these autoantibodies and to quantify these reactions with enzyme-linked immunosorbent assay are under way.

R. A. Moscicki (unpublished observations, 1990) has similarly found that 60% of patients with CPSNHL have antibody activity against type II collagen or a 60 kd protein isolated on SDS-PAGE. This 60 kd protein was thought to be a degradation product of type II collagen, because absorption of positive sera with type II collagen eliminated subsequent antibody activity against the 60 kd protein.

We have discerned a 30 kd protein band on gel electrophoresis of human cochlear tissue extracts. We do not believe this band represents a collagen fragment, as preparation of this tissue did not include pepsinization, and steps were taken to inhibit lysosomal proteolytic degradation. Furthermore, this protein migrated consistently faster than did the LMW fragment of type IX collagen. It is of great potential interest that three patients (50% of all patients with Meniere's disease in our study) had antibody binding to this protein as detected by Western blot; but after careful consideration of the patients' physical condition and clinical course, we could not draw any conclusions regarding the character of this protein or its role in Meniere's disease. Further studies to address these issues are under way.

The initial stimuli for the development of type II and IX collagen–specific immune responses leading to the production of autoantibodies seen in these diseases are a matter of speculation. It must ultimately result in the trimolecular interaction of 1) peptide 6 through 12 amino acids in length derived from endosomally processed collagen ("T cell epitopes"), 2) host MHC molecules, and 3) the T cell receptor. Implied in this is the importance of host MHC molecules. Indeed, the presence of human leukocyte antigen (HLA) DR3 (a class II MHC molecule) has been shown to increase the risk of developing inner ear diseases, including Meniere's disease, otosclerosis, and strial presbycusis. This risk is further heightened by the association of certain class I MHC molecules (A1 and B8) with HLA-DR3.[36] Also of paramount importance is the nature of the specifically reacting T cell receptor. Thus far, there is strong suggestion that there is restricted usage of Vβ gene (T-cell β-chain variable region gene) subsets in animal models of type II collagen–induced arthritis (T. J. Yoo et al, unpublished observations). Similar studies of T cell receptor gene restriction with respect to collagen-induced ear diseases are presently under way in our laboratory.

Previous animal studies strongly suggest that collagen-specific antibodies play a key role in the pathogenesis of tissue damage in some inner ear diseases. This study extends support for that notion within the human system, but practical difficulties in obtaining serial tissue biopsy specimens make similar studies in humans untenable. It cannot, therefore, be rigorously concluded on the basis of this or previous studies whether or not the type II and IX collagen– or cochlear protein–specific antibodies associated with these diseases are of critical importance to their pathogenesis or merely an epiphenomenon. Several studies have now demonstrated that remission of disease activity can be accomplished with intensive immunosuppressive therapy[5,6,11,12] (also J. J. Shea and T. J. Yoo, unpublished observations, 1982), indicating that while the exact nature of the immune defect(s) escapes us, (auto)immune inflammatory processes clearly contribute to the pathogenesis of these diseases.

ACKNOWLEDGMENTS — The authors thank Dr G. Gardner of Baptist Hospital, Memphis, Tennessee, and Dr D. Brackmann, House Clinic, Los Angeles, California, for providing the samples. At the 29th annual Inner Ear Biology Workshop (Engelberg, Switzerland, August 30–September 2, 1992) Dr J. Buji et al of Grosshadern Clinic, Munich, Germany, described higher levels of antibody to type II, type IX, and type XI collagen in patients with otosclerosis than in controls (abstract 18).

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SPONTANEOUS REMISSION IN EXPERIMENTAL AUTOIMMUNE LABYRINTHITIS

SHIGEHARU YAMANOBE, MD
TOKYO, JAPAN

JEFFREY P. HARRIS, MD, PHD
SAN DIEGO, CALIFORNIA

We investigated the time course of hearing impairment and cellular infiltration into the inner ear after systemic sensitization of guinea pigs with a single intradermal injection of bovine inner ear antigen (IEAg) in complete Freund's adjuvant (CFA). Lymphocytes and polymorphonucleocytes appeared mainly in the scala tympani on days 7 to 14, and in addition there was thickening and cellular infiltration of the round window membrane at day 14. These cellular infiltrations resolved after day 28. The auditory brain stem response thresholds from IEAg-sensitized animals were significantly elevated after day 7. Some sensitized animals (n = 5) had spontaneous remissions after day 28; however, the hearing thresholds did not completely recover. These results demonstrate that experimental autoimmune labyrinthitis can be induced by a single inoculation of IEAg-CFA and that remission, as evidenced by clearing of the cochlear cellular infiltration and improved hearing thresholds, can occur spontaneously.

KEY WORDS — autoimmune disease, deafness, inner ear, labyrinthitis, remission.

INTRODUCTION

Numerous experimental models of autoimmunity have been established to enhance our understanding of the underlying mechanisms and potential therapies of clinical autoimmune diseases. Examples of these models include experimental allergic encephalomyelitis (EAE), experimental allergic thyroiditis, experimental allergic neuritis, experimental myasthenia gravis, experimental arthritis, and experimental glomerulonephritis.

The sensitization protocols employed to establish these experimental autoimmune models often differ considerably, since the major manifestations of autoimmunity may be due to several different immunopathologic responses in the host, including delayed-type hypersensitivity, antibody-dependent cell-mediated cytotoxicity, immune complex disease, and so on. For example, EAE, a well-established animal model of autoimmune disease, is primarily the result of delayed-type hypersensitivity. Since 1947, EAE in most experimental animals has been regularly induced by a single injection of central nervous system (CNS) tissue or antigenic proteins (eg, myelin basic protein) emulsified with complete Freund's adjuvant (CFA).[1-3] This has resulted in EAE models in mice,[4-6] rats,[7] guinea pigs,[8,9] rabbits,[10,11] hamsters,[12] and monkeys,[13] which may undergo remission and relapse. In EAE, for instance, repeated boosts of antigen in incomplete Freund's adjuvant have not enhanced severity of encephalomyelitis, but rather caused suppression of the disease[14] and have been, in fact, employed clinically in the treatment of multiple sclerosis patients.[15,16] It has since become clear that repeated antigenic immunizations brought on suppression in EAE due to the induction of tolerance through suppressor T cells. Thus, if the autoimmune disease is primarily caused by cellular immunity, boosting with antigen may blunt the severity of the disease.

Many of the characteristics of immunity that are operative in the CNS appear, not surprisingly, to be similar for the inner ear, since it is an extension of the CNS. The concept of sequestered antigens isolated from systemic immunity by the blood-brain barrier has been extended to the inner ear through the recognition of a blood-labyrinth barrier, which in great part shields the inner ear from humoral immunity[17,18] and raises the question of whether cellular immunity plays a dominant role.

One of the distinctive features of both clinical (eg, multiple sclerosis) and experimental (eg, EAE) autoimmune conditions is the propensity for spontaneous

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From the Department of Surgery, Division of Otolaryngology–Head and Neck Surgery, University of California Medical Center, and the Research Service, Veterans Administration Medical Center, San Diego, California. Dr Yamanobe is currently at the Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan. This research was supported by grant DC 00193 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders and the Research Service of the Veterans Administration. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Veterans Administration Medical Center, San Diego.

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REPRINTS — Jeffrey P. Harris, MD, PhD, Division of Otolaryngology–Head and Neck Surgery, Veterans Administration Medical Center, V-112C, 3350 La Jolla Village Dr, San Diego, CA 92161.

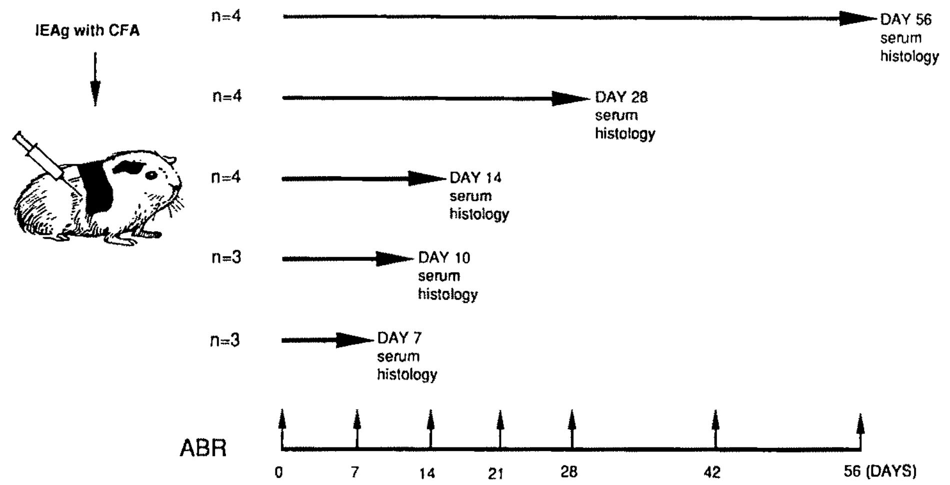

Fig 1. Experimental paradigm. IEAg — inner ear antigen, CFA — complete Freund's adjuvant, ABR — auditory brain stem response.

remissions and subsequent relapses. In the CNS of EAE animals, cellular infiltration is commonly seen 2 weeks following a single inoculation of antigen, with subsequent spontaneous disappearance.[9] Similarly, in patients with autoimmune inner ear disease, remission and relapse have been observed as part of their clinical picture.

In order to better define the spontaneous cause of experimental autoimmune labyrinthitis (EAL), we examined the histologic and physiologic events following a single injection of inner ear antigen in the guinea pig, a model previously shown to result in experimental autoimmune sensorineural hearing loss following serial antigenic immunizations.[19]

MATERIALS AND METHODS

Animals. A total of 30 female strain 13 guinea pigs weighing approximately 200 to 300 g and obtained from Charles River Breeding Farms, Wilmington, Mass, were used in this experiment. For all experimental procedures, each guinea pig was deeply anesthetized with a combination of sodium pentobarbital (Nembutal, 30 mg/kg) and fentanyl-droperidol (Innovar-Vet, 0.3 mL/kg).

Antigen. Fresh bovine temporal bones were obtained from an abattoir, frozen within 1 hour of harvesting at -20°C, and stored until dissection. After thawing at room temperature, the cochlear and vestibular membranous labyrinthine tissues were dissected from the temporal bones in approximately 20 minutes' time under microscopy, with care taken not to include bone dust or nonrelated tissues. The tissues were placed in chilled phosphate-buffered saline with aprotinin, phenylmethanesulfonyl fluoride, and ethylenediaminetetraacetic acid and kept frozen at -70°C until used. The tissues were then thawed at room temperature, teased apart, homogenized, and sonicated in 1% Triton X-100 in phosphate-buffered saline (PBS) and centrifuged at 2,500 rpm for 10 minutes. The supernatant was used as crude inner ear antigen (IEAg) for use in immunization and enzyme-linked immunosorbent assay (ELISA) determinations.

Immunization Protocols. At the outset of the experiment, guinea pigs were inoculated intracutaneously in multiple sites in the nuchal area with 0.2 mL of an emulsion consisting of equal parts of bovine IEAg and CFA (100 μg/0.1 mL). Control animals were inoculated in the same way, with saline instead of IEAg and CFA. No further immunizations were performed. The immunization protocols are summarized in Fig 1.

Immunoassay. Antibody levels to IEAg were determined by solid-phase ELISA. Micro-ELISA plates were coated with 100-μL volumes of IEAg at 2.5 μg/mL in coating buffer, by overnight incubation at 4°C. Unbound antigen was removed by washing three times in PBS containing 0.05% Tween 20 (PBS-T20). One hundred microliters of 3% gelatin was added to each well and incubated for 1 hour at room temperature. Diluted sample serum, containing 1% gelatin buffer containing 0.05% Tween 20, was added to each well for 2 hours at 37°C. Negative controls consisted of normal guinea pig sera or guinea pig sera injected with CFA only. Washing was repeated with PBS-T20, and bound antibody detected by incubating for 1 hour at 37°C with 100-μL volumes of a 1/5,000 dilution of horseradish peroxidase–conjugated rabbit anti guinea pig immunoglobulins in 1% gelatin buffer containing 0.05% Tween 20. After washing in PBS-T20 three times, 100 μL of the enzyme substrate (10 mg *o*-phenylenediamine, 10 μL of 30% hydrogen peroxide in 25 mL citrate phosphate buffer) was added and incubated in the dark. Thirty minutes later, the reaction was stopped with 2N sulfuric acid, and the intensity of color change was observed. The plates were read on a Micro-

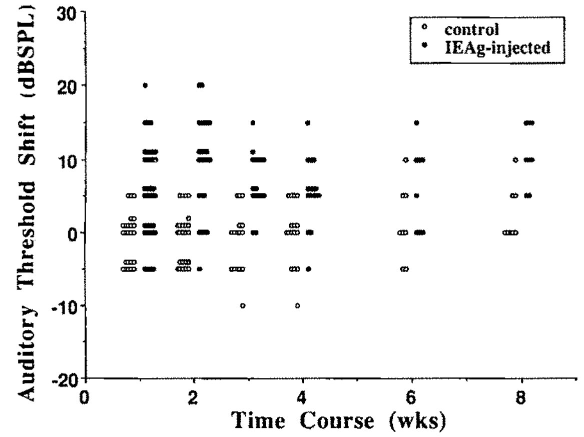

Fig 2. Auditory threshold shifts over time, measured by auditory brain stem response. SPL — sound pressure level.

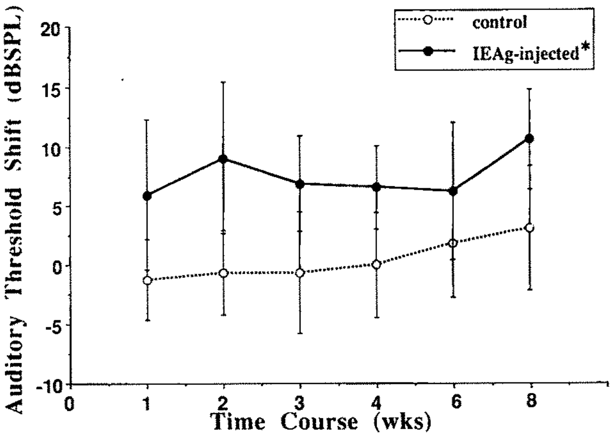

Fig 3. Comparison of ABR thresholds for control animals (16 ears) and IEAg-sensitized animals (16 ears) for 4 or 8 weeks following sensitization. * — IEAg-sensitized group differed significantly from controls ($p < .001$, two-way analysis of variance).

ELISA reader (Dynatech Diagnostic, Inc, South Windham, Me) with a 492-nm filter.

Auditory Evoked Brain Stem Response. Hearing was measured by auditory evoked brain stem response (ABR) using platinum subdermal needle electrodes without opening the tympanic bulla on days 0, 7, 14, 21, 28, 42, and 56 after sensitization. In brief, after sedation, the animal was placed in a double-walled booth. Grass needle electrodes (Grass Instrument Co, Quincy, Mass) were placed subdermally in the scalp midline (noninverting), posterior to the stimulated ear (inverting), and the midline of the abdomen (common). Bioelectric activity was amplified and filtered from 100 to 3,000 Hz with a Princeton Applied Research model 113DC-AC preamplifier and input to a Hewlett-Packard model 3561A wave analyzer. The ABRs were obtained by averaging the electroencephalogram to 256 stimulus preparations. Each ABR represented a time window of 16 milliseconds, obtained with a sampling frequency of 50 kHz. Clicks for stimulation were 100-microsecond electrical pulses produced by a Grass S88 stimulator. Clicks were presented at 3/s and routed through an attenuator to a Beyer DT 48 (2000) earphone. Click stimulus was presented initially at 50 dB sound pressure level (SPL), decreased in level by 10 dB while the response was observed clearly, and then decreased in 5-dB decrements until no response was observed. Threshold was defined as the lowest level at which a response was observed. At the threshold and 5 dB below the threshold, two sequences of recordings were obtained at each stimulus level and double-traced on a plotter so as to ensure reproducibility. The latency and amplitude of each wave were disregarded in this study; such factors would be influenced by variations in head size and differences in the electrode position in each measurement of ABR. Differences between group means of ABR thresholds were tested for significance ($p < .05$) by a computerized two-factor analysis of variance.

Histology. After we measured auditory thresholds and obtained sera for determination of antibody levels on the terminal day, the animals were killed painlessly by intracardiac perfusion with 5% paraformaldehyde in 0.1 mol/L sodium phosphate buffer, and the temporal bones were immediately removed and stored in cold fixative overnight, decalcified in phosphate-buffered 8% ethylenediaminetetraacetic

TIME COURSE OF HISTOLOGIC CHANGES WITHIN INNER EAR FOLLOWING SENSITIZATION WITH INNER EAR ANTIGEN

Days After Immunization	*Cellular Infiltration in Cochlea*	*Loss of Spiral Ganglion Cells*	*Macrophage Increase in ES*	*PMN Infiltration in ES*	*Cellular Infiltration in RWM**
7	3/6	0/6	3/6	0/6	0/6
10	2/6	0/6	3/5	0/5	2/6†
14	4/8	2/8	4/8	1/8	0/8
28	0/8	2/8	3/7	2/7	0/8
56	0/8	4/8	4/7	2/7	0/8

Data are numbers of affected ears per total ears.

ES — endolymphatic sac, PMN — polymorphonucleocyte, RWM — round window membrane.

*This occurred without evidence of middle ear infection.

†Control animals failed to show RWM changes (n = 4).

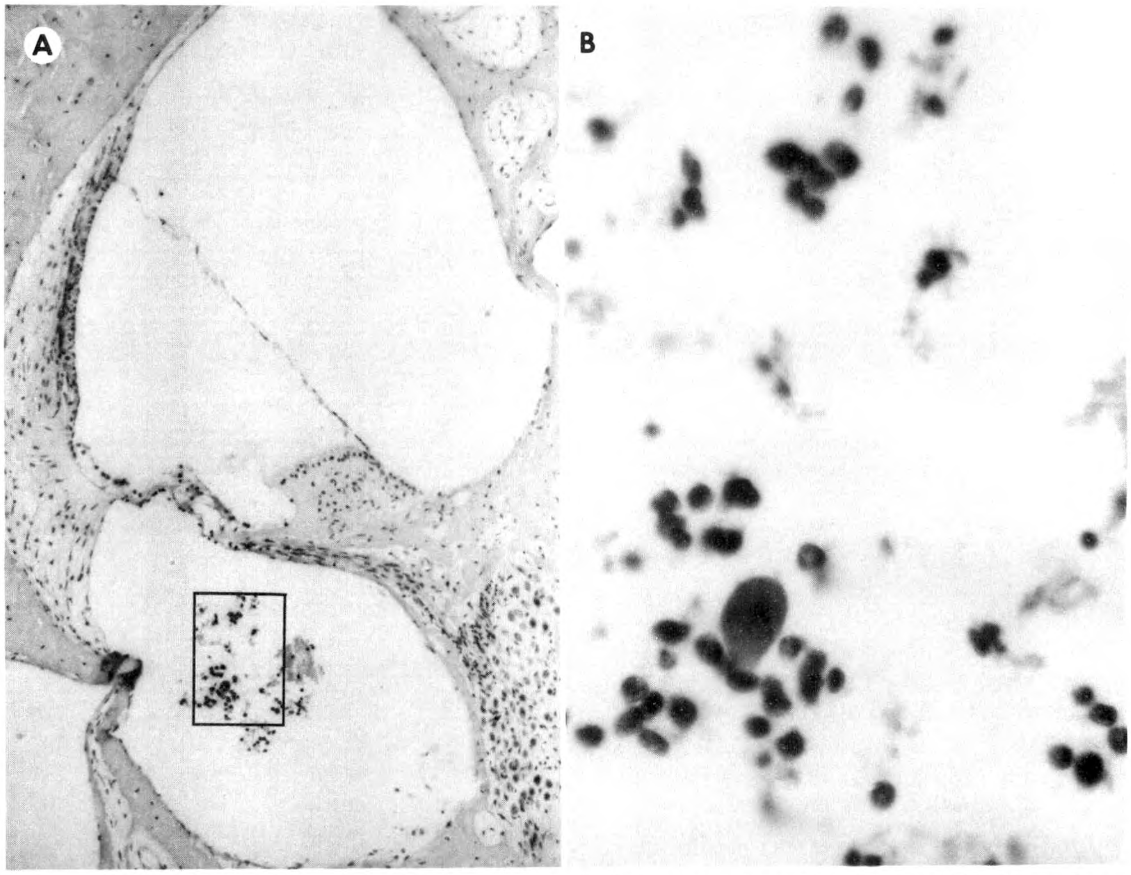

Fig 4. Section of cochlea from IEAg-sensitized guinea pig (H & E; day 14). A) Lymphocytes and polymorphonucleocytes are seen in scala tympani. B) Higher magnification (original x400) of boxed area in A.

acid, embedded in paraffin, and examined histologically with hematoxylin and eosin staining.

RESULTS

Hearing Threshold Changes. The hearing threshold shifts in all guinea pigs sensitized with IEAg at various time points are presented in Fig 2. The mean ABR threshold level of all guinea pigs before sensitization was 31.0 dB SPL in the IEAg-sensitized group (±5.9 SD) and 31.5 dB SPL in the control group (±4.5 SD). The ABR thresholds from IEAg-sensitized animals were elevated relative to control animals after day 7, and were greatest at day 14. The mean ABR threshold shift at day 14 was 9.7 dB SPL in the IEAg-sensitized group (±6.4 SD). Some animals (n = 5) sensitized with IEAg had spontaneous remissions after day 28; however, the hearing thresholds never completely recovered. Fifty percent of the animals sensitized with IEAg had bilateral hearing losses, and 25% of the animals had unilateral hearing losses with elevated thresholds 10 dB or greater above the presensitization thresholds.

Long-term survivors were examined at 4 or 8 weeks after sensitization, and the IEAg-sensitized group (n = 8) showed significant increases in ABR thresholds compared to the control group (n = 8; Fig 3, two-factor analysis of variance, $p < .001$).

Histology. Guinea pigs were painlessly killed on days 7, 10, 14, 28, and 56 after sensitization as described above. The histologic results are shown in the Table. Control guinea pig temporal bones, examined at days 14, 28, and 56 after sensitization, were unremarkable except for a few lymphocytes and a moderate number of macrophages seen in the endolymphatic sac (ES) lumen. The experimental animal temporal bones showed cellular infiltration in the inner ear. There were a moderate number of lymphocytes and polymorphonucleocytes (PMNs) in the scala tympani on days 7 through 14 (Fig 4). In some, the cellular infiltration into the scala tympani was limited to the corner of the scala tympani in the basal turn of the cochlea, adjacent to the modiolus. Additionally, there were increases of macrophages and PMNs in the ES lumen and in the perisaccular connective tissue by 7 days in almost all of the guinea pigs (Fig 5). Thickening and cellular infiltration of the round window membrane was seen at day 14 in two of the guinea pigs (Fig 6). Polymorphonucleocyte infiltration in the ES lumen and perisaccular space persisted in four animals 28 days following sensitiza-

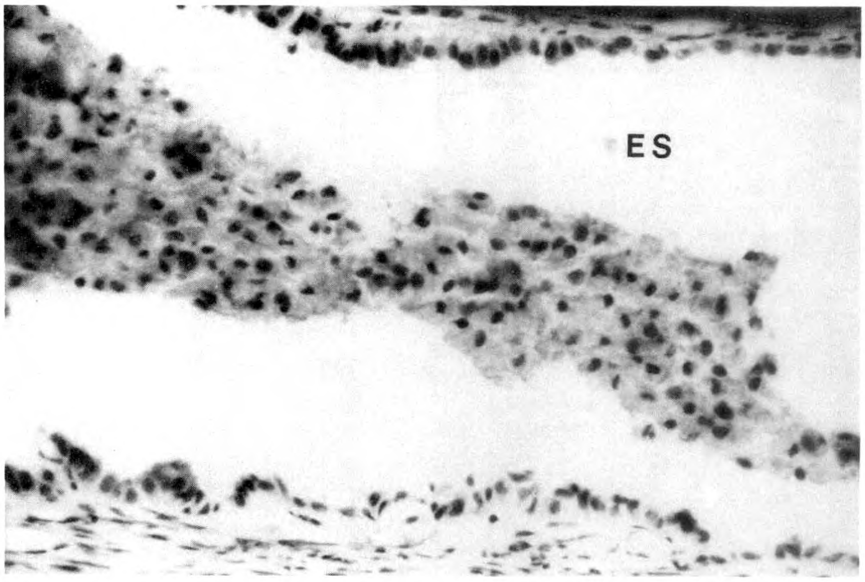

Fig 5. Endolymphatic sac (ES) of IEAg-sensitized guinea pig (day 10). Increase in macrophages is seen in lumen.

tion (Fig 7), while the cellular infiltration previously observed in the cochlea had disappeared. Several of the temporal bones showed scattered spiral ganglion cell degeneration, primarily located in the basal turn on days 14, 28, and 56 after sensitization. No hair cell loss was seen in any of the experimental animals.

Antibody Levels to Inner Ear Antigen. Mean serum anti-IEAg levels measured on day 14 showed a small but significant increase in anti-IEAg for the IEAg-sensitized group compared with the control group. By day 28, as mentioned previously, the hearing had improved, yet the antibody levels to IEAg were at their highest point during the observation period (Fig 8).

DISCUSSION

Beickert,[20] in 1961, first demonstrated EAL histologically, following sensitization of guinea pigs with isologous inner ear tissue. In 1964, Terayama and Sasaki[21] confirmed the development of EAL with histologic findings and alterations in Preyer's reflex in guinea pigs. Harada et al[22] demonstrated that endolymphatic hydrops could be produced by a type III allergic reaction. In these studies endolymphatic hydrops developed in guinea pigs following injections of rabbit stria vascularis in CFA, yet endolymphatic hydrops could not be produced in C4 complement–deficient guinea pigs.[22] In 1987, our laboratory demonstrated that sensitization of guinea pigs with bovine IEAg preparations in CFA induced an autoimmune labyrinthitis characterized by significant hearing loss, spiral ganglion cell degeneration, perivascular infiltration by plasma cells, edema, and hemorrhage.[19] This study confirmed the development of EAL electrophysiologically and histologically in guinea pigs and suggested the similarity of the experimental model to autoimmune sensorineural hearing loss (SNHL) seen clinically.[23,24] While delayed-type hypersensitivity was examined by performing lymphocyte transformation assays from spleen, lymph node, or peripheral blood lympho-

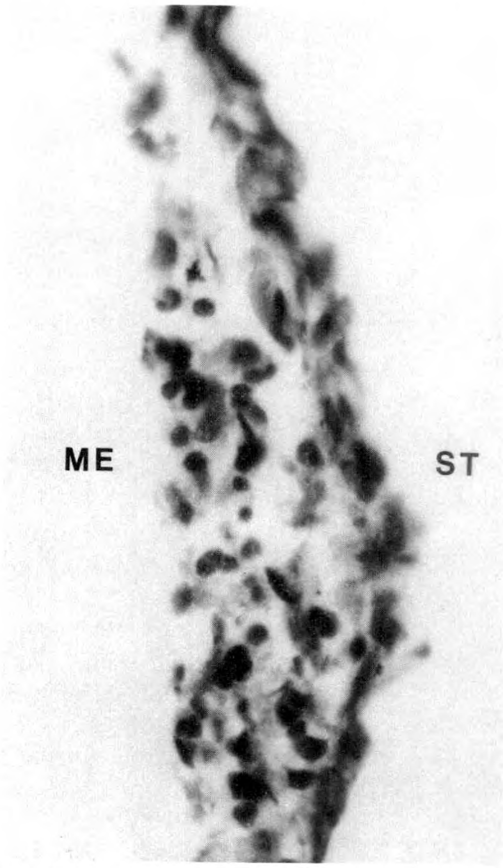

Fig 6. Thickening and cellular infiltration of round window membrane after IEAg sensitization (day 14). Polymorphonucleocytes, lymphocytes, and red blood cells were observed in middle layer. ST — scala tympani, ME — middle ear.

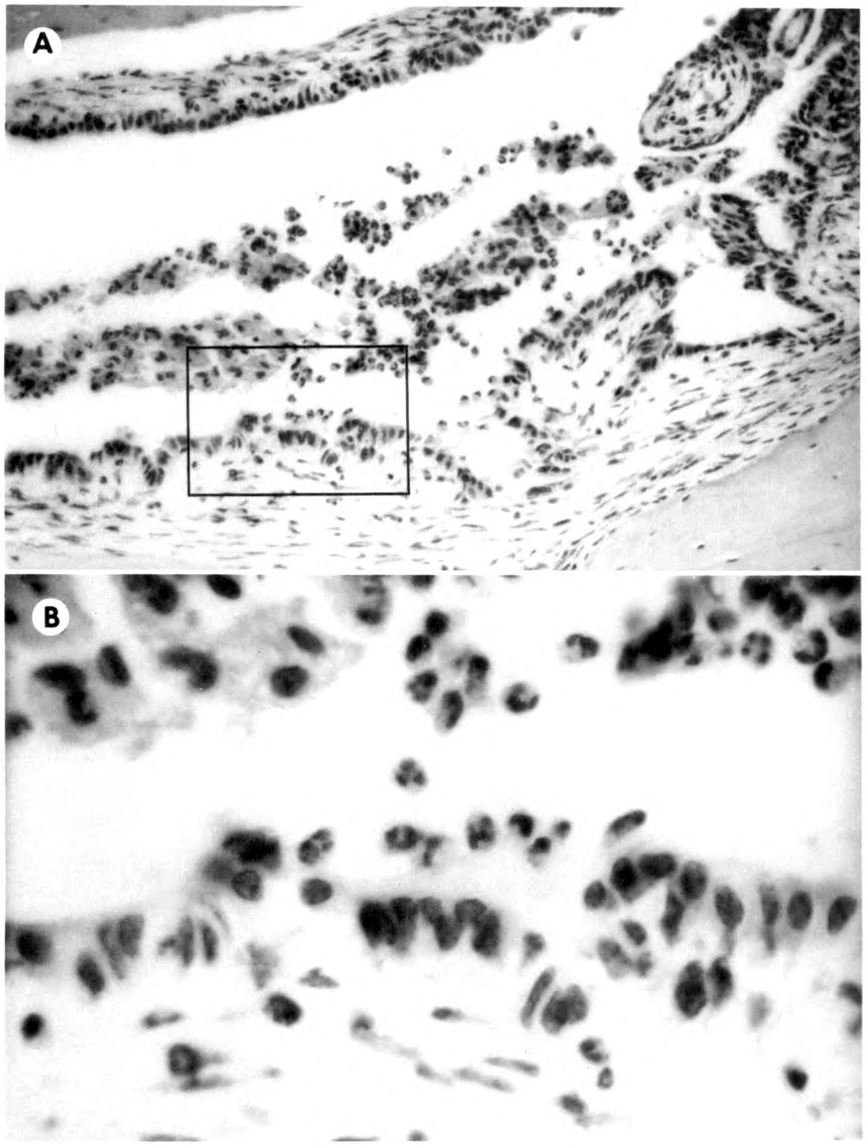

Fig 7. Section of endolymphatic sac after IEAg sensitization (day 56). A) Polymorphonucleocytes predominate within sac lumen. B) Higher magnification (original x400) of boxed area in A.

cytes, the majority of animals failed to show a proliferative response. Antibody titers in the immunized animals were uniformly elevated. Subsequently, we reported the presence of an autoantibody to one of the inner ear antigenic epitopes, with a molecular weight of 68,000 d, which both the EAL animals and patients with autoimmune SNHL both exhibited by Western blot analysis and two-dimensional gel electrophoresis.[25] These studies and others[26-29] have clearly established these models for the study of autoimmune deafness; however, the natural course of the experimental disease has not been adequately described with respect to remission and relapse, nor have the antigenic epitopes involved.

In the present study, following a single IEAg inoculation, we have demonstrated cellular infiltration in the cochlea, the ES, and the round window membrane in strain 13 guinea pigs. Previous investigators, using repeated immunization with antigen and incomplete Freund's adjuvant, have not observed cellular infiltration in the cochlea; this finding suggests that suppressor T cells may have been induced.[30,31] The induction of tolerance by this mechanism would also explain the lack of lymphocyte transformation reported in our previous study.[19] Examination of the temporal sequence of cellular infiltration within the inner ears of these animals is revealing. Early on in the course, two major events have taken place in the inner ear: 1) PMNs and lymphocytes have infiltrated into the scala tympani and 2) macrophages, the predominant cell found normally in the ES, are present in increased numbers. As the disease evolves, four further events occur: 1) cellular infiltration of the scala tympani clears, 2) the PMN population increases within the ES, 3) spiral ganglion cell degeneration develops, and 4) spontaneous remission of hearing loss occurs (in our study,

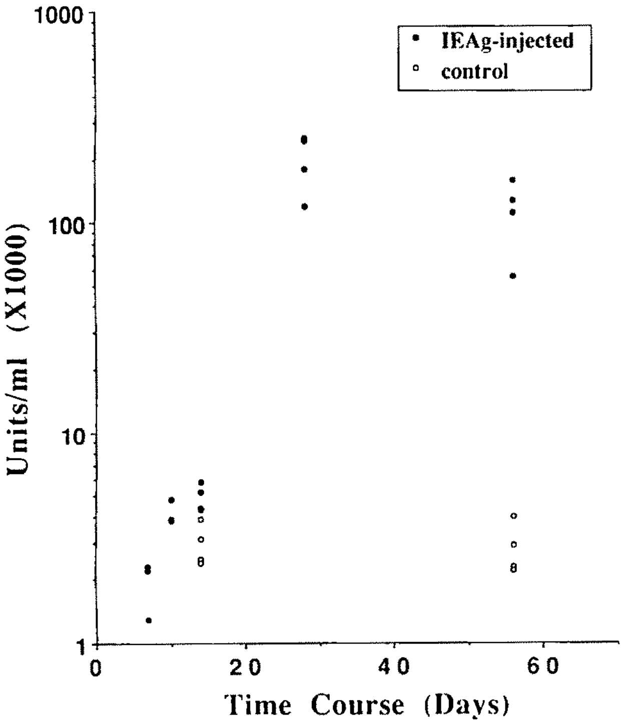

Fig 8. Results of enzyme-linked immunosorbent assay for anti-IEAg antibody in IEAg-sensitized and control groups.

at 28 days, but not back to normal thresholds, nor in all animals). These events suggest that an antigenic epitope within the inner ear has been targeted by the host's immune response, with subsequent mild inflammation developing. Damage and perhaps further antigen processing in the ES occur before the reaction dissipates.[32,33] Whether spiral ganglion cells are a direct target of the immune response or whether they become injured secondarily is unknown.

The cause of round window membrane thickening and its infiltration of inflammatory cells in the present model of EAL is unknown. Thickening and cellular infiltration of the round window membrane have been observed in animal models of suppurative otitis media,[34] otitis media with effusion,[35] and experimental otitis secondary to endotoxin instillation into the tympanic cavity.[36] Presumably, each of these causes has been the result of middle ear events irritating the round window membrane. Recently, however, Schuknecht[37] reported the temporal bone findings of a patient with progressive SNHL and systemic eosinophilia. This case of immune-mediated deafness was also associated with mononuclear cell infiltration and fibro-osseous organization in the region of the round window membrane in a fashion reminiscent of the animals seen in this study. Several mechanisms could be proposed for these findings: 1) the round window membrane might antigenically cross-react with bovine IEAg or the inciting antigen in autoimmune SNHL; 2) venous drainage through the vein of the round window might be impaired because of obstruction of the vein of the vestibular aqueduct[38]; or 3) inflammatory cells may have migrated directly from the capillaries in the round window membrane out into the scala tympani, or left the systemic circulation via the closely associated vein in a manner previously reported for cells entering the scala tympani through the spiral modiolar vein.[39]

The hearing impairment in EAL measured by ABR was greatest 14 days following IEAg sensitization. These electrophysiologic results correlated well with the histologic findings of cellular infiltration in the cochlea. At 28 days some of these animals went into remission, yet their anti-IEAg levels were at their highest; this finding suggests that the hearing deficits seen in these animals may have been triggered by cellular and not by humoral immunity. Further investigation of both the inciting antigen(s) and the cellular and humoral responses to it are now required in order to better interpret the experimental as well as the clinical situation.

It is clear that while the inner ear is isolated, it is not an immune-privileged site. It can engage in and be the target of immunologic reactions. As in all immune-mediated disorders, cellular infiltration is one of the hallmarks of the response. Further research is needed to ascertain what role cellular immunity plays in this disorder clinically, and why tests of cellular immunity have not proven sensitive in the diagnosis of autoimmune SNHL up to now,[19,40,41] despite several reports to the contrary.[42,43]

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SOFTWARE REVIEW

COCHLEAR ANATOMY: A MACINTOSH TOUR

Authors: Peter Santi and Eric Webster.
Company: Intellimation, PO Box 1922, 130 Cremona Dr, Santa Barbara, CA 93166-1922;
phone (800) 685-2100.
Hardware requirements: Macintosh with 2 megabytes of RAM operating system, version 6.0 or greater. Hard disk drive recommended.
Software requirements: Macintosh HyperCard System 1.2.2.
Price: $55.

This cochlear anatomy program is an outstanding example of the potential education application of computers. It deserves the highest possible rating and should be used by every otolaryngology resident during training, as well as by medical students and other health professionals working in the communicative disorders field.

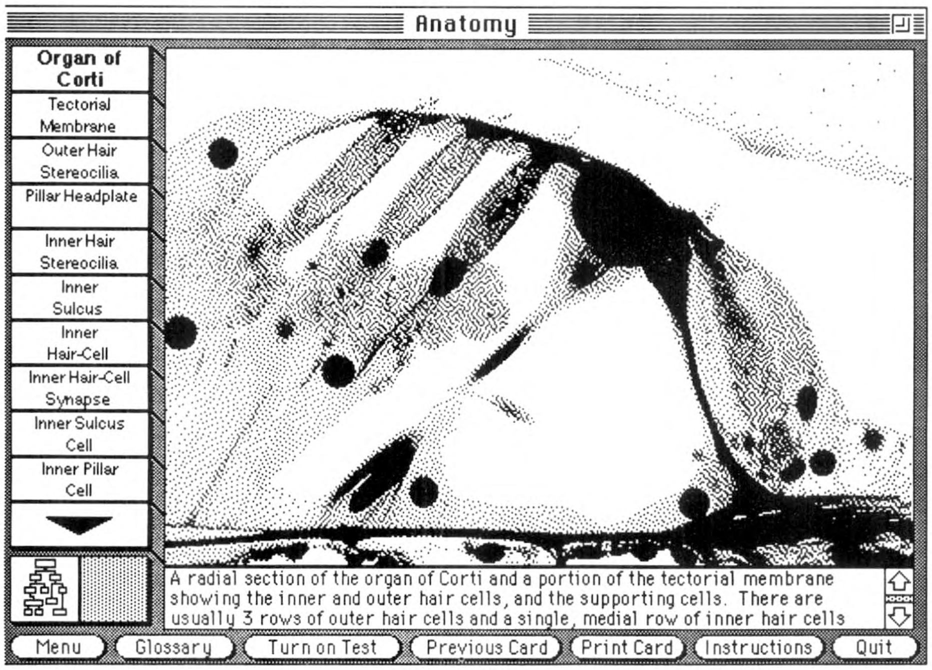
The program uses Macintosh's HyperCard System. This program is not available on IBM. The HyperCard System requires versions later than 1.25. HyperCard allows one to browse through a series of screens, much as one might look through index cards. Highlights can be placed on the screen by clicking a button so that part of the anatomy, magnified views, tonal sounds, or test questions can be brought up relating to a particular feature. The HyperCard System is good for teaching anatomy because it is easy and enjoyable to use.

There are several minor problems, however. First, the program runs in a black and white mode. It would be much more effective if it were a color program. Second, many of the on-screen buttons are turned on by simply moving the pointer over the button. This feature is unfamiliar to most Macintosh users, who are more accustomed to actually clicking the mouse over the button to make it work. In addition, despite the fact that the left side of the screen has a listing of the highlighted items, the location of each item is not readily apparent. Also, at times the left column indicates the next screen that is available to the user. Finally, the last criticism that I have is that the tone bursts, which are demonstrated in the last screen on the program, did not run properly. Only the very low-frequency tones could be appreciated with even the most updated version of the Macintosh. These are only minor problems with the overall program.

The cochlear anatomy program is divided into three general sections: anatomy, histologic methods, and sound basics. The anatomy section is the most elaborate, with screens that review nearly every detail of the cochlear anatomy. The user begins with an animal model; in fact, this program was developed as an alternative to the use of laboratory animals to teach cochlear anatomy and was funded by a grant for that purpose. After first visualizing the chinchilla itself, the user then has the opportunity to see the skull of the animal in the dorsal, lateral, and ventral views. Then the bulla of the temporal bone is opened, and the otic capsule is visualized. From there, a midmodiolar section through the cochlea is demonstrated. Some of the features of the midmodiolar section include the spiral ganglion, the vestibular membrane, the basement membrane, the vascularity of the stria vascularis, the spiral limbus, the tectorial membrane (Fig 1), Claudius' cells, and the spiral prominence. There is a more close-up view of the organ of Corti, which clearly shows inner and outer hair cells, the pillar headplate, sulcus cells, etc. Each of these structures can then be more carefully investigated through additional screens that highlight the important anatomic features of each. On completing the anatomy section, the user should have a complete grasp of the subject of cochlear anatomy.

The second section reviews the histologic methods for preparing the otic capsule for study of the anatomy. This section has screens that show scanning electron microscopy of the inner and outer hair cells, as well as a section on the methods for adding chemicals, preparing slides, and staining the slides. Some of this information will not interest the otolaryngologist, but this section is short and many of these points are animated, so that it is not a tiresome task to make it through the section.

The final section covers the concepts of sound basics, including the definition of sound, waveforms of sound, and demonstration of intensity and fre-



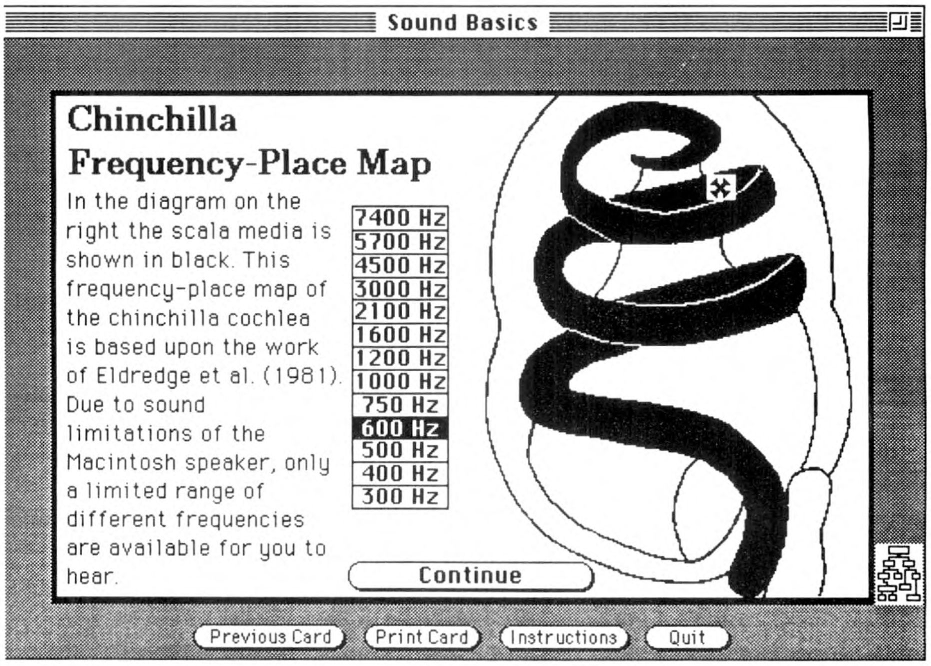
A radial section of the organ of Corti and a portion of the tectorial membrane showing the inner and outer hair cells, and the supporting cells. There are usually 3 rows of outer hair cells and a single, medial row of inner hair cells

Figure 1.

quency. There is a frequency place map at the cochlea, which is demonstrated with tones and their various locations in the cochlea (Fig 2). There is a demonstration of the effects of sound cancellation and of beating sounds. There is also a very nice section regarding the use of different filters and their effects on sound quality. This information is intended to demonstrate some of the difficulties that patients with high- or low-frequency hearing loss experience. There is also an interesting demonstration of tinnitus. Following the completion of the sound basics section, the student should have the basic concept of a tone and how it is coded by the cochlea.

Another interesting feature of the program is that there are accompanying questions built in. All of the questions are directed toward specific screens and specific anatomic structures. They help to complete the student's grasp of the cochlear anatomy and are an interesting part of the learning process.

Finally, there is a very helpful manual that besides explaining how to set up and run the software and use the program, has a glossary of all of the concepts and structures identified in the program. There is an extensive list of references for additional study. I would recommend this program to every otolaryn-



Chinchilla Frequency-Place Map

In the diagram on the right the scala media is shown in black. This frequency-place map of the chinchilla cochlea is based upon the work of Eldredge et al. (1981). Due to sound limitations of the Macintosh speaker, only a limited range of different frequencies are available for you to hear.

Figure 2.

gology resident, audiology student, and otology fellow, as it will simplify their acquisition of this crucial knowledge. I wish this program had been available when I was a resident.

MITCHELL K. SCHWABER, MD
Nashville, Tennessee

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6TH INTERNATIONAL CONGRESS ON INTERVENTIONAL ULTRASOUND

The 6th International Congress on Interventional Ultrasound will be held Sept 7-10, 1993, in Copenhagen, Denmark. For further information, contact Christian Noisse, Congress Secretary, Department of Ultrasound, Herley Hospital, University of Copenhagen, DK-2730 Herley, Denmark.

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20TH INTERNATIONAL CONFERENCE ON COCHLEAR IMPLANTS

The 20th International Conference on Cochlear Implants will be held June 23-25, 1993, at the Ritz-Carlton Hotel, San Francisco, California. For further information, contact University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; (415) 476-4251.

Ann Otol Rhinol Laryngol 101:1992

IMAGING CASE STUDY OF THE MONTH

MASSIVE OSTEOLYSIS (GORHAM'S DISEASE) OF THE TEMPOROMANDIBULAR JOINT

R. MARVIN FREEDY, MD
BIRMINGHAM, ALABAMA

KENNETH A. BELL, MD
NEW ORLEANS, LOUISIANA

Gorham's disease, also known as massive osteolysis or vanishing bone disease, is seen in young adults, affecting the axial or appendicular skeleton. Various sites of involvement have been described, including the pelvic bones, shoulder girdle, clavicle, ribs, hands, feet, skull, spine, and mandible. The disease is of unknown cause and involves proliferation of vascular fibrous tissue replacing normal bone. We now present an unusual case of massive osteolysis of the temporomandibular joint with tomographic, angiographic, and computed tomographic scan analysis, as well as clinical and pathologic correlation.

CASE REPORT

The patient is a 31-year-old man presenting at the Ochsner Clinic in the Department of Oral Surgery upon referral from a local dentist. He complained of preauricular pain over the left temporomandibular area for the last 2 years. There was no history of trauma and no history of arthritis. He had had no ear infections or facial injuries to the left side of the face. No medical treatment or other type of treatment had been instituted at his visit to the Department of Oral Surgery. Associated with his pain were occasional headaches. He had described, especially while chewing, a "wiggly jaw" and a "bone on bone" feeling. He noticed his jaw to be shifted more to the left; this trait was initially noted by his wife about 3 years prior to his visit. He described occasional ringing in the left ear, but hearing was normal.

Clinical examination revealed a deformity on the left side of the face and deviation of the mandible to the left side. There was tenderness over the joint, and the external auditory canal was within normal limits. Muscles were tender over this region. Interincisal opening of 45 mm was present, with a right lateral deviation to 7 mm and a left lateral deviation to 7 mm.

The radiographic examination included x-ray studies done elsewhere (not shown) that revealed significant degenerative joint disease and loss of the normal contour of the temporomandibular joint on the left. This appeared to involve both the condyle and the glenoid fossa.

Initial pluridirectional tomograms of the left temporomandibular joint area showed an absence of a mandibular condyle and destruction of the glenoid fossa region and the middle cranial fossa floor (Fig 1). In light of these findings, it was decided to undertake computed tomography (CT) of the base of the skull, which revealed similar findings plus erosion and destruction of the floor of the middle fossa back to and including the apex of the left petrous bone (Fig 2). This study was done with contrast, and no abnormal enhancement was noted. An arteriogram was then performed of the left carotid system, including separate internal and external carotid injections. This study revealed an avascular mass that caused

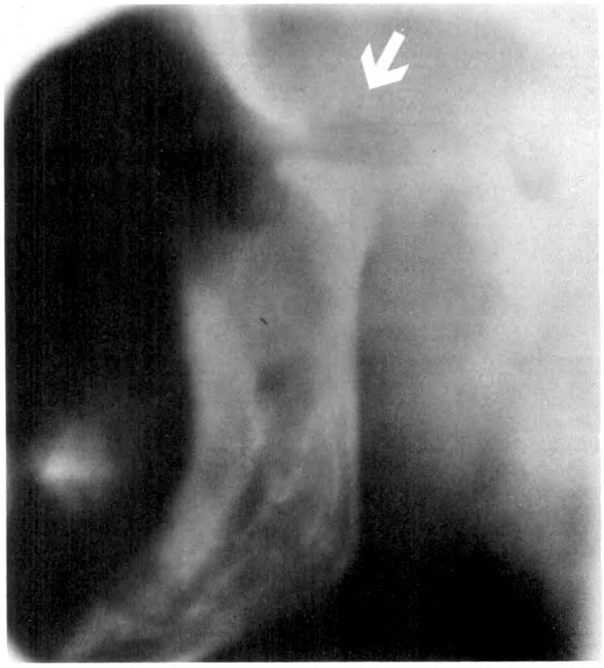

Fig 1. Pluridirectional tomogram of left temporomandibular joint showing destruction of mandibular condyle and glenoid fossa region (arrow).

From the Department of Radiology, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, Louisiana.

REPRINTS — R. Marvin Freedy, MD, Dept of Radiology, University of Alabama–Birmingham, 619 S 19th St, Birmingham, AL 35233.

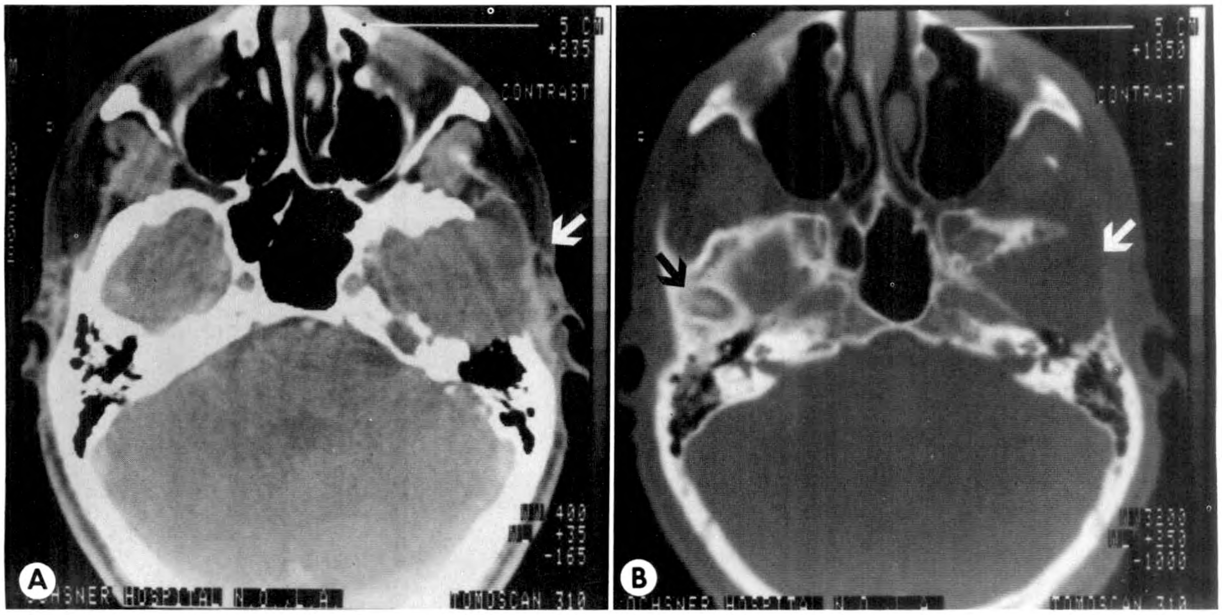

Fig 2. Computed tomograms of skull base with A) soft tissue and B) bone window settings showing destruction of left temporomandibular joint region and erosion of floor of middle cranial fossa back to left petrous temporal bone (white arrows). Note normal right temporomandibular joint region (black arrow).

stretching of the branches of the external carotid (Fig 3A). There was no supply to this area from the internal carotid (Fig 3B).

This case is somewhat unusual in that the destructive process and the focus of the tumor mass on the arteriogram were somewhat more lateral than one would expect with a glomus tumor, although this latter diagnosis was entertained as a possibility. In light of the radiographic findings, it was decided that a biopsy should be attempted. The lack of hypervascularity made this seem a reasonable approach.

On the basis of the clinical and radiographic findings, a surgical approach for biopsy was undertaken in the left preauricular region. At biopsy, a large amount of venous bleeding was encountered, but an adequate specimen was obtained.

Pathologically, the fragments of bone obtained from biopsy showed gaping, thin-walled, nonneoplastic blood vessels, with some showing irregularities of the walls of the type seen with arteriovenous malformations. This appeared to represent a nonneoplastic angiomatosis of the temporal bone with areas of reactive endothelial cells. In light of the massive degree of osteolysis and the radiographic finding that the probable center of the process was the temporal bone, the lesion was diagnosed as Gorham's disease or massive osteolysis of the temporomandibular joint.

DISCUSSION

Gorham's disease[1] is distinctly uncommon and has no sex predilection, but occurs predominately in the third and fourth decades. It is characterized histologically by an abundance of thin-walled venous capillary–size blood vessels in bone with eventual complete replacement of bone by fibrous connective tissue, also containing an increased number of capillaries. No cause for this disease has been determined, although a history of trauma is common and may trigger the process. Patients often present with weakness and limitation of movement, but not pain.[2]

Skeletal involvement is nearly always monocentric, and adjacent bones are involved by direct spread. The proliferating thin-walled, endothelial-lined capillary or sinusoidal vascular channels are histologically benign, but may invade adjacent soft tissue with associated destruction. Chronic lesions may develop extensive fibrosis. Osteolysis of bone occurs in a progressive, regional manner, with the bone simply "melting away."[2] Radiographically, early changes of focal intramedullary and subcortical lucency resembling osteoporosis are seen. Subsequently, concentric reduction of the bone gives a tapering appearance that resembles a "licked stick of candy."[3,4] Bony sclerosis is usually absent and fracture of an affected bone is often seen.[5] Severe cases may show complete dissolution of the involved bone on plain film radiographs.

Disability from the precipitated skeletal abnormality may be severe to incapacitating. The disease has an unpredictable course and may spontaneously arrest or progress relentlessly, with death occurring within 2 years. In those cases involving the chest wall, chylothorax has been reported as the lethal

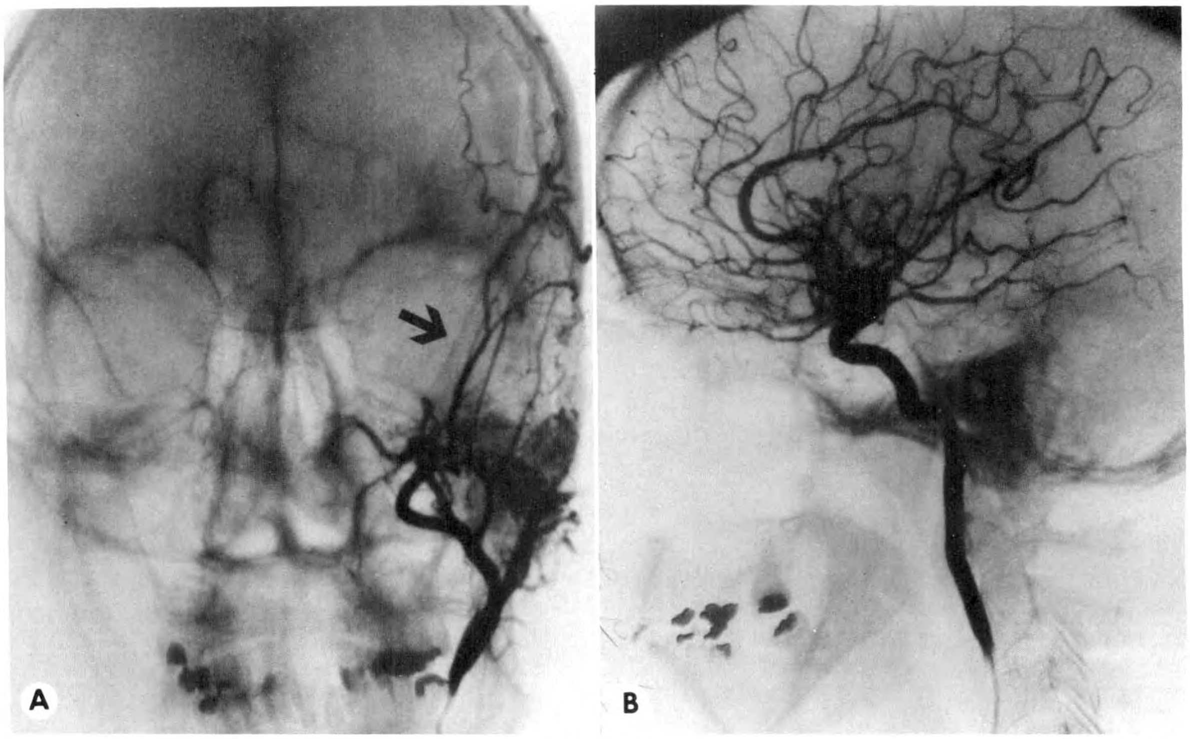

Fig 3. Left carotid arteriograms. A) Left external carotid artery injection (anterior-posterior view) shows stretching of branches of external carotid artery with avascular mass (arrow). B) Left internal carotid artery injection (lateral view) shows no internal carotid artery branches to mass.

event.[2]

Differential diagnostic considerations of Gorham's disease include skeletal angiomas, angiosarcomas, essential osteolysis, and hereditary osteolysis.[3,6] Histologically, Gorham's disease is distinct from these entities in having vascular channels lined by a single layer of flattened epithelial cells.[3]

Many different therapeutic regimens have been tried unsuccessfully in the treatment of Gorham's disease. These regimens have included estrogens, androgens, magnesium, calcium fluoride, adrenal extracts, ultraviolet irradiation, and ionized calcium.[4] Radiotherapy has been shown to have limited success,[7] as has surgery with bone replacement.[8] In our case, surgical debulking and packing was performed, with good healing of the soft tissues and no further bone destruction identified 9 months postoperatively.

A multiplicity of locations are affected by Gorham's disease, most frequently the shoulder girdle and hips. Mandibular involvement has been documented — but to our knowledge, no cases specific for the mandibular condyle articular surface and adjacent glenoid fossa. This case brings forth Gorham's disease as an important clinical consideration in patients with symptoms referable to the temporomandibular joint, particularly if there is an antecedent history of trauma, and adjunct radiographic findings to support this diagnosis.

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Ann Otol Rhinol Laryngol 101:1992

IMAGING CASE STUDY OF THE MONTH

CYSTIC SQUAMOUS CELL CARCINOMA METASTATIC TO THE NECK FROM OCCULT PRIMARY

J. P. WENSEL, MD, PHD
TUCSON, ARIZONA

J. MICHAEL TALBOT, MD
PORTLAND, OREGON

INTRODUCTION

Magnetic resonance imaging (MRI), with its high tissue contrast and multiplanar capability, has been shown to be a valuable modality for the evaluation of head and neck neoplasms. Recently, gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA)–enhanced MRI has been shown to be very useful in the evaluation of head and neck tumors.[1] The addition of fat suppression to T1-weighted Gd-DTPA–enhanced sequences often provides improved conspicuity and definition of both the primary and metastatic neoplasms.[2,3]

Patients who present with squamous cell carcinoma metastatic to cervical lymph nodes usually have a visible and/or palpable lesion on examination. Occasionally, no primary lesion can be found even with panendoscopy and blind biopsies of the nasopharynx, tonsil, and tongue base. In most series, the nasopharynx is the most common source of the occult primary lesion; the tongue base, tonsil, pyriform sinus, and skin represent less common sites of origin.[4,5]

Rarely, the nodal metastasis will present as a cystic mass in the anterior cervical triangle near the angle of the mandible. If the otolaryngologic examination is negative, these cystic masses are often misdiagnosed as branchial cleft cysts and are excised only to reveal a cystic, necrotic squamous cell carcinoma metastatic to an upper jugular chain node.[5] We recently studied two patients in whom Gd-DTPA–enhanced MRI performed with T1-weighting and fat suppression correctly identified the location of the occult primary lesion.

CASE REPORTS

Case 1. A 41-year-old woman was first seen in August 1988 complaining of a painless, right-sided, cystic-feeling neck mass. This was thought to be a branchial cleft cyst and was excised from the subdigastric region of the right side of the neck. Histologic findings at that time were consistent with branchial cleft cyst. Three years later the patient developed a second cystic right-sided neck mass in the right posterior triangle. The otolaryngologic findings were otherwise normal. The patient was a nonsmoker and nondrinker. The cystic mass was excised and proved to be necrotic squamous cell carcinoma metastatic to the cervical lymph nodes.

Prior to panendoscopy, an MRI scan was performed (Fig 1). The T1-weighted Gd-DTPA–enhanced axial images with fat suppression demonstrated an area of asymmetric enhancement deep in the tongue base on the right side. Biopsy of this region demonstrated squamous cell carcinoma.

Case 2. A 38-year-old man presented with a cystic-feeling mass in the right upper anterior triangle of the neck. The otolaryngologic examination yielded normal findings, and a needle aspirate of the lesion revealed fluid consistent with a diagnosis of branchial cleft cyst. A computed tomography (CT) scan was done that revealed a solitary cystic mass 2 cm in diameter in the right subdigastric region. The mass was excised and proved to be necrotic squamous cell carcinoma metastatic to a cervical lymph node.

An MRI scan (Fig 2) demonstrated a subtle asymmetric enlargement of the right faucial tonsil that contained a small area of nonenhancement. This was best demonstrated on the T1-weighted Gd-DTPA–enhanced axial images with fat suppression. On the basis of this information, the tonsil was excised despite completely normal findings on physical examination. A small occult squamous cell carcinoma was found in the deep tissues of the tonsil.

DISCUSSION

These two cases illustrate the efficacy of Gd-

From the Department of Diagnostic Radiology, Oregon Health Sciences University, Portland, Oregon. Dr Wensel is currently at the Department of Diagnostic Radiology, University of Arizona Medical School, Tucson, Arizona.

REPRINTS — J. Michael Talbot, MD, Dept of Diagnostic Radiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098.

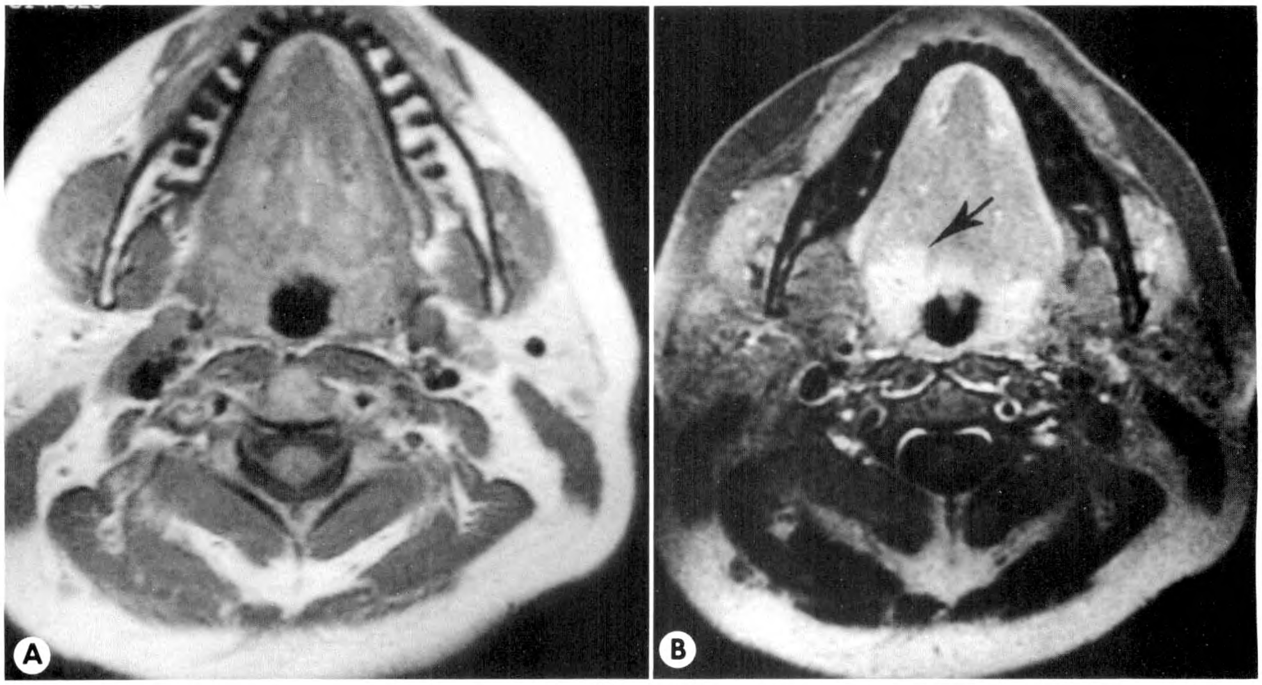

Fig 1. (Case 1) A) Axial T1-weighted magnetic resonance image through tongue base. Lesion in right side of tongue base is not readily apparent. B) Gadolinium-enhanced T1-weighted image obtained with fat suppression algorithm clearly demonstrates asymmetric enhancement deep in right side of tongue base (arrow). Biopsy of this region demonstrated squamous cell carcinoma.

DTPA–enhanced, fat-suppressed MRI for the detection of clinically occult squamous cell carcinomas. Although the MRI findings in both cases were very subtle, the specific knowledge that cystic squamous cell carcinoma metastases are nearly always from the tonsil or tongue base, coupled with these findings, directed surgical biopsy to the correct area. Case 2 failed to show the primary lesion on a CT scan; hence, the superiority of MRI over CT was illustrated in this instance. Furthermore, neither lesion was well seen on the unenhanced MRI sequences. In both cases it was felt that the Gd-DTPA–enhanced, fat-suppressed

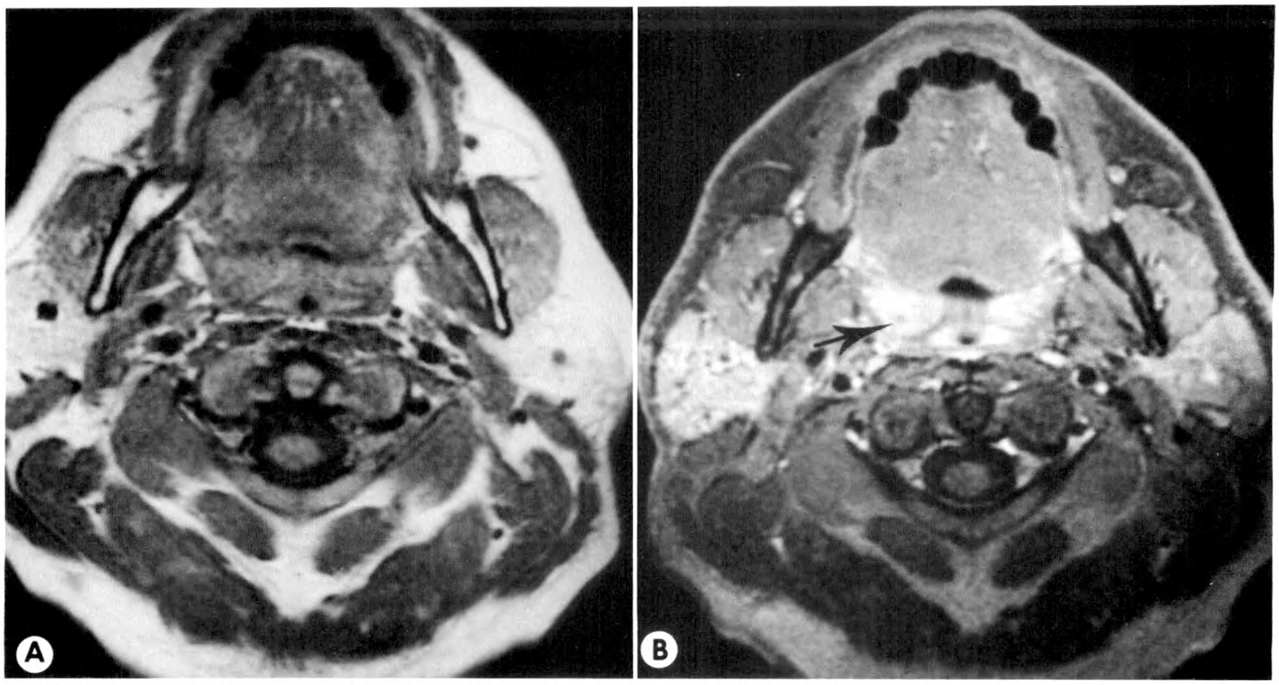

Fig 2. (Case 2) A) Conventional T1-weighted axial image obtained at level of faucial tonsils. Suggestion of tonsillar asymmetry is discernible. B) T1-weighted image with gadolinium enhancement and fat suppression better defines asymmetry suggested in A, and reveals small focus of nonenhancement within right faucial tonsil (arrow).

images provided the most diagnostic information, in agreement with the findings of previous authors.[2,3]

The histologic examination of the cystic neck metastases in these two cases demonstrated no convincing evidence that they were carcinomas arising in branchiogenic cysts. The current opinion is that carcinoma arising in a branchiogenic cyst is either extremely rare or perhaps nonexistent. The late occurrence of the second metastatic episode in case 1, 3 years after the first cystic metastasis was removed, is not unusual. Micheau et al[5] reported on 27 patients with cystic squamous cell carcinoma metastases to the neck. The primary lesion in the tonsil or tongue base was not discovered in 6 of the 27 until 3 or more years had passed. Their experience also suggests that these patients have a better prognosis than the patient with larger tonsillar and tongue base carcinomas and solid neck metastasis.

Precise localization of the primary tumor is valuable in patients with cystic neck metastasis, allowing for a more informed consideration of treatment options that generally include radiotherapy with or without surgery. If the nasopharynx can be eliminated as a possible source of primary lesions, the morbidity associated with irradiation of this region can be avoided.

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PATHOLOGY CONSULTATION

NONSQUAMOUS CARCINOMAS OF THE LARYNX

JOHN G. BATSAKIS, MD
MARIO A. LUNA, MD ADEL K. EL-NAGGAR, MD, PHD
HOUSTON, TEXAS

Nonsquamous carcinomas make up fewer than 1% of all epithelial malignancies of the larynx. The majority are subsurface in origin and arise from seromucous glands of the larynx. Adenoid cystic carcinoma is not only representative of this group, it is the most prevalent. All other salivary-type carcinomas are rare. Rarer still are surface adenocarcinomas. Neuroendocrine carcinomas appear to constitute the majority of so-called laryngeal adenocarcinomas.

No more than 1% of the epithelial malignancies of the larynx are nonsquamous in type (Table 1[1-6]). This low incidence makes them even less common than their counterparts in the sinonasal tract. Like those higher in the airway, the neoplasms can be imperfectly separated into ones that are surface and ones that are nonsurface (seromucous gland) in origin. In the larynx, the subsurface carcinomas outnumber the surface-origin nonsquamous carcinomas by a very considerable margin, with adenoid cystic carcinoma the most frequent and most readily recognized. The histologic equivalent of the papillary low-grade surface adenocarcinoma of the paranasal sinuses must be exceedingly rare. The present authors have never seen one.

SUBEPITHELIAL AND INTRAEPITHELIAL GLANDS

The sites of origin of the nonsquamous carcinomas of the larynx follow the anatomic distribution of the larynx's subepithelial glands and the intraepithelial mucous glands. Approximately two thirds of the adenoid cystic carcinomas are in the subglottis. The other nonsquamous carcinomas, in contrast, are rarely subglottic, with supraglottic and transglottic involvement being nearly equal.

The subepithelial glands are part of the mucociliary system of the laryngeal mucosa and are either purely mucous (usually small and tubular) or larger and branched tubuloalveolar seromucous glands. Secretory end-pieces are asymmetrically arranged around the duct system.

The number, distribution, and density of the glands in macroscopically normal adult laryngeal mucosae have been described by Bak-Pedersen and Nielsen, and the following is derived from their studies.[7-9] There is an increase in the median gland count from the subglottis, to over the glottis, to the supraglottis: 263, 271, and 371, respectively. The subglottic glands extend anteriorly and posteriorly from the lower border of the cricoid cartilage, without any differences in transition from the trachea, cranially up to the most medially prominent part of the vocal cord. The glottic area shows a considerable variation in gland count. The highest numbers are in the floor of the sinus of Morgagni and in the false vocal cord. The lowest count is in the true vocal cord. The presence of glands centrally on the surface of the vocal cords is rare. Glands are found quite anterior in the anterior commissure or posteriorly toward the arytenoid region. In the supraglottis, the greatest number of glands are in the false cords, the aryepiglottic region, and, anterior, at the caudal part of the epiglottis. The aryepiglottic folds and the most cranial part of the epiglottis contain the fewest glands.

The overall density of glands in the intrinsic larynx has been estimated to be between 23 and 47 glands per square centimeter. The lower part of the glottic region shows the greatest differences in density: 13

TABLE 1. NONSQUAMOUS CARCINOMAS OF LARYNX

Authors	*No. of Laryngeal Neoplasms*	*No. of Laryngeal Nonsquamous Carcinomas*	*%*
Whicker et al[1]	3,100	27	0.9
Spiro et al[2]	2,793	14	0.5
Ferlito[3]	2,052	21	1.0
Sessions et al[4]	888	9	0.1
Eschwege et al[5]	1,342	5	0.4
Cohen et al[6]	2,967	18	0.6
Total	13,142	94	0.7

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

TABLE 2. "ADENOCARCINOMA" AND ADENOID CYSTIC CARCINOMA OF LARYNX

Characteristic	*"Adeno-carcinoma"*	*Adenoid Cystic Carcinoma*
No. of patients	50	33
Male to female ratio	1:11	3:1
Age at diagnosis (y)	46-80 (mean 63)	29-75 (mean 48)
Location		
Supraglottis	37	11
Subglottis	8	18
Glottis	0	2
Transglottic	5	2
Metastases to cervical lymph nodes at first presentation	30 (60%)	6 (18%)
Death because of carcinoma	33 (66%)	9 (27%)
Average survival of patients dying of carcinoma (mo)	17.5 (range 3-69)	49.4 (range 12-79)

Cases collected from references 1, 2, 5, 6, 12-18.

glands per square centimeter on the vocal cords to 128 per square centimeter on the false vocal cords and medial wall of Morgagni's sinus. The greatest concentration of glands is in the saccule (139 glands per square centimeter), and this region is also the one with the greatest median density (82 glands per square centimeter). There is a very low density of glands in the extrinsic laryngeal regions (epiglottic vallecula, pyriform recess, postcricoid region), with the valleculae and pyriform recess having the most constant occurrence and density.

Intraepithelial glands are distinct from subepithelial glands. A typical intraepithelial gland is made up of 15 to 30 mucus-secreting cells with a structure like that of goblet cells. They extend from the epithelial surface down toward the basement membrane, on which they may rest, but which they do not penetrate. The cells are radially placed around a narrow lumen that extends to the epithelial surface, where it debouches in a narrow stoma. Irregularly distributed in the larynx, intraepithelial glands are most numerous in the supraglottis and least numerous in the subglottis. In any laryngeal region the glandular areas measure from 0.25 to 60 mm^2 (median 4 mm^2). There is a significant negative correlation between the occurrence of intraepithelial glands and that of subepithelial glands in the supraglottis.

NONSQUAMOUS CARCINOMAS

Except for adenoid cystic carcinomas, salivary-type carcinomas are rare in the larynx. Even pleomorphic adenomas are almost curiosities in the larynx. Immunocytochemical methods have now appropriately classified as neuroendocrine neoplasms many types formerly included under the generic heading of adenocarcinoma.[10] These in turn are subtyped as typical or atypical carcinoids and small cell neuroendocrine carcinomas.[10]

For mucopidermoid carcinomas, there are no specific techniques to help establish the diagnosis. Pathologists have to rely on subjective interpretations based on a histologic similarity to mucoepidermoid carcinomas of the major and oral salivary glands, a taxonomically ambiguous intracellular mucin, or worse, extracellular mucoid changes to support a diagnostic impression. The finding of mucin within cells of a mucosal or submucosal neoplasm is not enough to frame a diagnosis of mucoepidermoid carcinoma.

Damiani et al[11] have suggested there is a continuum of laryngeal surface carcinomas: 1) non–mucin-producing squamous cell carcinoma, 2) squamous cell carcinoma with unicellular mucin production, 3) mucoepidermoid-adenosquamous carcinoma, 4) adenocarcinoma with variable degrees of squamous metaplasia, and 5) pure adenocarcinoma. The combining of mucoepidermoid carcinoma with adenosquamous carcinoma reflects the difficulty surgical pathologists have in distinguishing between these two carcinomas in mucosae.

Even considering the two carcinomas as a diagnostic unit, it is evident that they are uncommon neoplasms in the larynx. In their report of 21 mucoepidermoid-adenosquamous carcinomas from the Armed Forces Institute of Pathology (AFIP) files of 1945 to 1979, Damiani et al[11] indicated there had been only 32 previously reported cases in the world's literature.

If the histologic appearances permit, it is important to separate the mucoepidermoid-adenosquamous carcinoma group into high and low grades because of the marked differences in prognosis. Eight of the 21 AFIP neoplasms were called low-grade mucoepidermoid carcinomas. (The descriptions and photomicrographs are appropriate.) Nine, according to the authors, were more appropriately considered adenosquamous carcinomas than mucoepidermoid carcinomas. By an actuarial method, the 3-, 5-, and 10-year survival for all of the low-grade mucoepidermoid carcinomas was 100%, regardless of clinical stage (6 of the 8 were stage 1 or 2). For the adenosquamous–high-grade mucoepidermoid carcinomas, the survival followed clinical stage and grade, and was 53% at 3 years posttherapy.

On the basis of our own experience and that of the AFIP, it is safe to presume that except for low-grade mucoepidermoid carcinomas, other supposed grades of that carcinoma in the larynx are much more likely to be adenosquamous carcinomas.

The requirement for an adenocarcinoma and a squamous cell carcinoma to be present in the same neoplasm with readily light-optic demonstrable intercellular bridges and keratinization in the squamous carcinoma component should reduce possible confusion with mucoepidermoid carcinoma. A nearly constant presence of an in situ or superficial squamous cell carcinoma also points to an adenosquamous carcinoma. Adenosquamous carcinomas have the property of involving the surface mucosa, an ability rarely seen in mucoepidermoid carcinomas. Adenosquamous carcinomas are usually deeply invasive and manifest a decided tendency to shed their squamous phenotype and to become more like a poorly differentiated adenocarcinoma in the deep parts of the neoplasm.

There is also a frustrating lack of clarity in what constitutes an "adenocarcinoma" of the larynx after exclusion of adenoid cystic carcinoma. From the literature one gets the distinct impression that the so-called adenocarcinomas are poorly differentiated, large, bulky, and preponderantly supraglottic neoplasms that are subsurface in origin. When photomicrographic illustrations are available, many, if not most, have a neuroendocrine appearance. At the risk of comparing "apples and oranges," we present in Table 2[1,2,5,6,12-18] data on laryngeal adenocarcinomas and adenoid cystic carcinomas.[12-18] We have excluded tumors labeled mucoepidermoid or adenosquamous carcinoma from the adenocarcinoma group.

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ANNUAL INDEX

AUTHORS

Abbas PJ, 496
Akino T, 491
Akyildiz N, 699
Albers FWJ, 679
Alvi A, 487
Antonelli PJ, 977
Arandia H, 799
Arfken CL, 105
Aronson AE, 511
Arriaga MA, 955
Atlas MD, 620
Austin JR, 76

Bacon CK, 147
Bagger-Sjöbäck D, 437
Bagot D'Arc M, 669
Bailey CM, 465, 595, 656
Baldwin DL, 168
Bard MC, 578
Batsakis JG, 102, 185, 282, 367, 455, 540, 623, 710, 794, 879, 958, 1024
Baum PA, 876
Bauwens LJJM, 479
Bayramoglu I, 699
Beamis JF Jr, 556
Bell KA, 1018
Benecke J, 280
Benton NC, 92
Berenholz LP, 827
Berger-Vachon C, 42
Berke GS, 567, 883
Bernstein JM, 87, 848, 1000
Berson S, 861
Bhuiya T, 487
Biller HF, 888
Bishop MJ, 583
Blalock D, 142
Blamey PJ, 342
Bless DM, 237
Bluestone CD, suppl 155:58
Boeckx WD, 265
Boedts D, 931
Bond G, 222
Borrow JA, 275
Boyd EL, 628 (book review)
Brackmann DE, 955
Braga AM, 590
Brandwein M, 798 (letter to editor)
Bredenkamp JK, 472
Brodsky G, 156
Brodsky L, 87
Broekaert D, 931
Brons EN, 635
Brook I, suppl 155:9
Brookes GB, 665
Brown AM, 342
Brownlee RE, 293; 798 (letter to editor)
Bruns MD, 778
Brusis T, 390
Buckingham RA, 755
Burgess LPA, 95
Burggraaff BA, 183
Burton DM, 742
Butsch RW, 67

Callender DL, suppl 155:16
Campbell KCM, 176, 403, 496
Carranza AP, 328
Carrillo R, 367
Carter DM, 861
Ceisler E, 763
Chan KH, 248
Chanaud CM, 832
Chapman JC, 459
Chapman PH, 939
Cheney ML, 763
Cheung DT, 328
Cho GJ, 659
Cho JS, 1000
Clark GM, 342
Clark KF, 870
Clary RA, 598
Clayman GL, 909
Cohen SR, 328
Collan Y, 982
Collet L, 42
Cooper DS, 76
Corlieu P, 669
Cornelisse CJ, 635
Costantino PD, 807
Cotton RT, 731
Coucke P, 931
Cousins V, 525
Crockett DM, 472
Crumley RL, 472
Cunningham MJ, 363, 598, 791

Daculsi G, 669
Dagan R, 866
Dalley RW, 452
Darrell J, 156
Davis KR, 939
Davis PJ, 375
Dayton V, 119
Dedo HH, 81, 216
De Groot JCMJ, 479
Delaere PR, 265
DeMaria TF, 607
Dewanjee MK, 961
Dillon WP, 876
Divis BO, 776
Djedou B, 42
Dohar JE, 469
Dolan KD, 100, 360, 617, 705
Dolgin SR, 209
Dowell RC, 342
Doyle WJ, 248
Dudley JP, 472
Duncan S, 372 (letter to editor)
Dunham ME, 916
Duvall AJ III, 458 (obituary); 469, 977

Eavey RD, 598, 939
Eckel HE, 113, 629
Eid NS, 372 (letter to editor)
El-Naggar AK, 102, 185, 540, 710, 879, 1024
Epstein JS, 961
Eriksen C, 827
Evans JNG, 465, 595, 656

Faden H, 87
Fagan PA, 620
Feehs RS, 142, 222
Ferguson WS, 939
Fitzgerald DC, 459
Flint PW, 583
Fliss DM, 866
Ford CN, 237
Forsen JW, 333
Frankenthaler R, 958
Freedy RM, 1018
Freeman DT, 782
Freeman FJ, 67
Frei F, 994
Friedman CD, 807
Friedman M, 897
Frijns JHM, 635
Fujita A, suppl 157:4; 759
Fujita F, 675
Fujiyoshi T, 1000
Fukuda H, suppl 157:78
Fukuda S, suppl 157:67
Funasaka S, 32
Furman JMR, 643
Furstenberg AC, 20

Gacek RR, 691
Ganz WI, 961
Gates GA, suppl 155 (ed):4, 24; 105, 724
Gatot A, 707
Gavilán C, 339
Gavilán J, 339
Gaylis B, suppl 155:24
Gelber RH, 261
George EF, 888
Gerratt BR, 567, 883
Gersdorff M, 669
Gibson SE, 46
Giebink GS, suppl 155:21
Gittelman PD, 190 (book review)
Gmelig-Meyling F, 679
Godberson GS, 770
Goksu N, 699
Goldenberg JL, 724
Gonzalez C, 95
Goodman ML, 763
Goodwin WJ, 961
Gordon M, 342
Gotoh Y, suppl 157:54
Gould SJ, 815
Gray SD, 408
Green DC, 883
Greenberg E, 161
Gregor FA, 854

Grobman L, 961
Guelinckx PJ, 265
Gulya AJ, 459

Haberkamp TJ, 38
Haberman PJ, 920
Haberman RS II, 920
Hain TC, 255
Hamaguchi Y, suppl 157:26
Hammerschlag MR, 371 (letter to editor)
Hansmann ML, 770
Hara M, 612
Harada T, suppl 157:72; 437
Harker LA, 403, 496
Harre RG, 705
Harris FP, 994
Harris JP, suppl 157:67; 1007
Harrison GA, 375
Harvey J, 105
Hashida Y, 248
Haughey BH, 105, 333, 724
Hauser R, 994
Hayashi M, 759
Haziroglu R, 699
Hendrix RA, 147
Herranz J, 339
Himi T, suppl 157:21
Hirano M, 138
Hirsh FA, 827
Hoffman HT, 946
Hogikyan ND, 724
Hokunan K, suppl 157:58
Hollow RD, 342
Holmgren G, 546
Hom DB, 349
Honda K, 32
Honjo I, suppl 157:4; 759
Hooper R, 525
Hornung DE, 229
Horowitz JB, 51
Houston G, 807
Hozawa K, suppl 157:82
Huizing EH, 479, 679

Ichimiya I, suppl 157:39
Iida M, 685
Iino Y, suppl 157:16
Ikezono T, suppl 157:54
Inglis AF Jr, 61
Inuyama Y, suppl 157:67
Iritani H, 423
Isaacson G, 372 (letter to editor)
Ishikawa K, suppl 157:67
Ishikawa T, suppl 157:78
Ito E, suppl 157:7

Janfaza P, 939
Johnson JT, 807
Joliat T, 1000
Juhn SK, 437
Jung TTK, 395

Kaga K, 413
Kaga T, 685
Kakiuchi H, suppl 157:32
Kaneda N, suppl 157:39
Kanematsu S, 413
Kanzaki Y, suppl 157:78
Karademir N, 699
Kardatzke D, 248
Kataura A, suppl 157:21; 491
Katoh Y, suppl 157:32
Katz NM, 872
Katz RM, 742
Kawano J, 32
Kawauchi H, suppl 157:39
Kearns DB, 742
Keenan MJ, 778
Keithley EM, suppl 157:67
Kemaloglu Y, 699
Kim H-N, 659
Kim YM, 659
Kinoshita K, suppl 157:32
Kitajima K, 675
Kitzes-Cohen R, 161
Kiukaanniemi H, 982
Kobayashi K, 491
Koda J, 127
Kodama H, suppl 157:21
Koike S, suppl 157:82
Koltai PJ, 371 (letter to editor); 560
Komatsuzaki A, 355
Komiyama S, 519
Kondraske GV, 67
Korol HW, 92
Koufman JA, 142
Krohn KA, 395
Krueger BL, 417
Krug M, 1000
Kryzer TC Jr, 95
Küçük B, suppl 157:67
Kudo K, suppl 157:7, 16
Kudoh S, 519
Kumakawa K, 32
Kumar NR, 209
Kumazawa T, suppl 157:63
Kumoi T, 423
Kurata K, suppl 157:4
Kuroiwa Y, 138
Kurono Y, suppl 157:11
Kusakari C, suppl 157:82
Kyogoku M, suppl 157:82

Lallone R, 627 (book review)
Lalwani AK, 261
Lane B, 931
Lashmet FH, 20
Lathrop F, 20
Laurell GFE, 969
Lauretano AM, 791
Lavedan P, 909
Lawrence M, 191; 797 (obituary)
Lee C-C, 665
Lee SY, 270
Leh JF, 770
Leiberman A, 866
Leigh I, 931
Leopold DA, 229
Leperque S, 931
Li C-W, 525
Lian G, 328
Liebsch N, 939
Lim DJ, 607
Lin AN, 861
Linke RP, 770
Lipton RJ, 578
Lizak M, 961
Lo WWM, 955
Loftus JM, 237
Ludlow CL, 127, 832
Luna MA, 102, 540, 710, 1024
Lundman L, 437
Lusk RP, 135
Lyon MJ, 691

Maas C, 280
Mahnovski V, 328
Mair EA, 300
Maisel RH, 119, 349
Majoor MHJM, 679
Makielski KH, 275
Maloney BP, 691
Mambrino LJ, 51
Maniglia AJ, 209
Manning SC, suppl 155:42
Maragos NE, 321
Marais J, 665
Mark AS, 459
Martin DS, 280
Masuyama K, suppl 157:78
Matsui K, 519
Matsunaga T, suppl 157:72
Matsune S, 163, 750
Matsuoka H, 138
Maves MD, 503, 778
Mayer AD, 897
McBride TP, 872
McCabe BF, 1, 543 (editorials); 946
McCaffrey TV, 578
McCulloch TM, 583
McGuirt WF, 142, 222
McKenna JA, 216
McKinney WM, 222
Medoff G, suppl 155:5
Meidan N, 866
Merida M, 872
Meyer W, 161
Michel O, 390
Miller JM, 168
Miller RP, 916
Miller SK, 395
Minatogawa T, 423
Ming Y, 567
Miyake H, 685
Miyamura K, suppl 157:78
Miyazaki H, 519
Mizoguchi H, 519
Mogi G, suppl 157 (ed):11, 39
Montgomery WW, 763
Moon SK, 659
Morgon A, 42
Morizono T, 437
Morris HL, 503
Mortelliti AJ, 731
Moscicki RA, 688
Mueller DP, 100
Muntz HR, suppl 155:24; 135
Myer CM III, 731
Myssiorek D, 487

Nadal D, 848
Nadol JB Jr, 988
Nakamura A, 607
Nakazawa M, suppl 157:7
Namon AJ, 538
Narayanan K, 807
Natividad M, 567
Natori Y, suppl 157:16
Nechtman CM, 626, 628 (book reviews); 954
Nelson-Drake J, 459
Nimni ME, 328
Nishimura Y, 423
Nomura Y, 612
Nonaka M, suppl 157:54
Nuss DW, 807
Nuttall AL, 168
Nuutinen J, 982

Ochi JW, 465, 595, 656
Ogata T, 685
Ogino S, suppl 157:72
Ogra PL, suppl 157:7; 87, 848
Ohde S, 413
Ohlsén KA, 168
Ohtani S, 491
Okamoto Y, suppl 157:7
Okamura H, 383
Oliveira CA, 590
Ostfeld EJ, 445
Ostyn F, 265
Overholt EM, 452

Panje WR, 538
Panossian D, 395
Pappas DG, 189, 626, 627, 628 (book reviews)
Paradise JL, suppl 155:33, 51
Park YM, 395
Parnes LS, 176
Parsons DS, 300
Patel G, 255
Patel JA, suppl 157:7
Perelman N, 328
Pignatari S, 408
Pohl J, 67
Pototschnig C, 629
Pransky SM, 742
Prasad S, 872
Probst R, 994
Proctor CA, 797 (obituary)
Proetz AW, 11, 715
Pyman BC, 342

Quiney R, 560

Ramaekers FCS, 479, 931
Ramig LO, 511
Rarey KE, 601
Rauch SD, 430, 688
Rautiainen M, 982
Raymond AK, 455, 794
Rebeiz EE, 556
Reilly JS, 739
Ricciardelli EJ, 275
Richardson MA, 583
Richtsmeier WJ, suppl 155:46
Riley DA, 310
Rimell F, 119
Rinehart RJ, 617, 705
Roark RM, 67
Rodriguez-Peralto JL, 367
Roski RA, 705
Rothstein SG, 190, 628 (book reviews)
Rudert H, 770

Saito T, 491
Sakagami M, suppl 157:72
Sakai M, 685
Sakakura Y, suppl 157:26
Samonte BR, 950
Sandefur J, 395
Sanders I, suppl 156; 888, 893
Sando I, 163, 750, 841, 925
SanMartin J, 688
Sano M, suppl 157:72
Santi PA, 437
Sato K, 138
Sato M, 685
Savage HE, 909
Savage MM, 403
Schaefer SD, 67
Schantz SP, 909
Schechtman KB, 724
Schläpfer E, 848
Schmall RJ, 360
Schmidt PH, 635
Schor RH, 643
Schumann TL, 643
Schwaber MK, 38, 1015
Schwob JE, 229
Sculerati N, 190 (book review)
Seid AB, 742
Seltzer S, 459
Senturia BH, 18
Sercarz JA, 567
Sewall EC, 285
Seyer J, 1000
Shapshay SM, 556
Shemen L, 798 (letter to editor)
Sheridan ML, 3 (introduction)
Shibata A, 413
Shim YJ, 659
Shimamura K, suppl 157:11
Shimizu N, 519
Shiroma M, 32
Shirotori K, suppl 157:7
Shive C, 408
Shockley WW, 293; 798 (letter to editor)
Silber SR, 511
Silberberg A, 445
Silva DA, 893
Slavit DH, 321, 578
Sloman-Moll E, 950
Smith AE, 503
Smith EM, 408
Smith ME, 472, 731
Smyth LT Jr, 92
Sneige N, 185, 282, 623, 794
Snyderman CH, 807
Soh N, 848
Stanievich J, 87
Stanley RB, 76
Stein EH, 363
Strauss M, 310
Strickland HL, 222
Strome M, 156, 950
Strome S, 156, 950
Suzuka Y, suppl 157:63
Suzuki T, suppl 157:21
Swarts JD, 248
Swearingen B, 939

Tabata T, suppl 157:32
Tago C, suppl 157:87
Takahashi H, suppl 157:4; 163, 750, 759, 841, 925
Takahashi M, suppl 157:58
Takasaka T, suppl 157:82
Takezawa H, suppl 157:21
Talaat M, 501
Talbot JM, 1021
Talmi YP, 946
Tami TA, 261
Tanaka S, 138
Taylor DL, 909
Teitelbaum SL, 977
Ten Cate WJF, 601
Terpstra HL, 635
Thomsen J, 821
Thornburg JD, 530
Thumfart WF, 113, 629
Todd NW, 417
Togawa K, suppl 157:7
Tomiyama S, suppl 157:48, 54
Tomoda K, suppl 157:63
Toriyama M, suppl 157:16
Tos M, 821
Tovi F, 707
Troughear RH, 375
Tsuzuku T, 413
Turek LP, 408
Turgut S, 821
Turner J, 620

Uno K, suppl 157:78
Updike C, 530
Uri N, 161

Van Blitterswijk C, 607
Van Demark DR, 503
Van Der Gaag R, 679
Van Der Mey AGL, 635
Van Dulken H, 635
Van Muijen G, 931
Van Pelt F, 127
Vandamme B, 265
Varvares MA, 763
Veldman JE, 479
Vergos K, 556
Viner TF, 617

Wagner DV, 61
Wald ER, suppl 155:37
Wallace M, 135
Walter MA, 739
Ward PH, 883
Ward RF, 205, 861
Watabe T, 685
Watanabe K, 355

Watkins JL, 46
Watson BC, 67
Weber AL, 363, 791, 939
Weber PC, 371 (letter to editor)
Weber RS, suppl 155:16
Weeks D, 395
Weinstein GS, 183
Welsh JJ, 854
Welsh LW, 854
Wenig BL, 46
Wensel JP, 1021
Wever EG, 191
Weymuller EA, 452
Wiese JA, 617
Williams JC, 472
Winholtz WS, 511
Winkworth AL, 375
Winn HR, 452
Wolf GL, 248
Woo P, 314, 799
Woolley AL, 724
Wu B-L, 888
Wu J, 156, 950
Wykoff TW, 209

Xu W-Z, 988

Yagi T, suppl 157:54
Yamanaka N, 32, 491
Yamanobe S, 1007
Yamashita T, suppl 157:63
Yamawaki T, suppl 157:63
Yanagihara N, 383
Yanagisawa E, 51
Yanagisawa K, 51
Yanagita N, suppl 157:87
Ye XJ, 1000
Yoo TJ, 1000
Yoshida T, 138
Young G, 909
Young M, 815
Young Y-H, 612
Youssef M, 821
Yuh WTC, 100
Yukawa K, 32
Yumoto E, 383
Yuo A, suppl 157:16

Zalzal GH, 651
Zaretsky LS, suppl 156
Zimbler M, 888
Zorowka P, 629

SUBJECTS

Abducens interneurons
  Quantitative ultrastructural study of cat abducens interneurons, 691

Abscess
  Radiographic analysis of deep cervical abscesses, 854

Acoustic neuroma
  Causes of facial nerve paresis after translabyrinthine surgery for acoustic neuroma, 821
  Recovery from repeated sudden hearing loss with corticosteroid use in presence of acoustic neuroma, 827

Acyclovir
  Herpes zoster oticus: treatment with acyclovir, 161

Adenocarcinoma
  "Adenocarcinoma, not otherwise specified": diminishing group of salivary carcinomas, 102
  Laryngeal adenocarcinoma, not otherwise specified, treated with carbon dioxide laser excision and postoperative radiotherapy, 920

Adenoid
  Adenoidectomy and otitis media, suppl 155:24
  Immunologic response of adenoidal lymphocytes to respiratory syncytial virus, 848

Airflow
  Airflow study of pathologic larynges using constant temperature anemometer: further experience, 675

Airway collapse
  Pediatric tracheobronchomalacia and major airway collapse, 300

Allergy
  Type I allergy in inner ear of guinea pig, suppl 157:78

Allograft
  Histopathologic correlates of acute laryngeal allograft rejection in rat model, 156

Ampulla
  Planum semilunatum of rat: new light and electron microscopy observations, 601

Amyloid
  Amyloidosis in upper aerodigestive tracts, 794
  Organ-limited laryngeal amyloid deposits: clinical, morphological, and immunohistochemical results of five cases, 770
  Primary salivary gland amyloidosis causing sicca syndrome, 487

Amyotrophic lateral sclerosis
  Rapid voice tremor, or "flutter," in amyotrophic lateral sclerosis, 511

Anaerobes
  Diagnosis and management of anaerobic infections of head and neck, suppl 155:9

Anatomy
  Anatomy of guinea pig temporal bone, 699
  Cochlear anatomy: Macintosh tour, 1015

Anemometer
  Airflow study of pathologic larynges using constant temperature anemometer: further experience, 675

Anesthesia
  Influence of general anesthesia on transiently evoked otoacoustic emissions in humans, 994

Aneurysm
  Aneurysm of anterior inferior cerebellar artery producing hearing loss, 705

Angiofibroma
  Spontaneous regression of juvenile nasopharyngeal angiofibroma, 469

Angiogenic growth factors
  Angiogenic growth factors: their effects and potential in soft tissue wound healing, 349

Annals Classic
  Forty questions in otolaryngology. (Suggestion box for young investigators), 715
  Ménière's symptom complex: medical treatment, 20
  Surgical removal of sphenopalatine ganglion. Report of three operations; elaborating original technic to expose pterygopalatine fossa, command internal maxillary artery and its

  terminals and infraorbital nerve and its branches, 285
  The surgery of otosclerosis, 546
  Transmission properties of middle ear, 191

Annals memorabilia, 1892-1991, 3

Antibiotics
  Antibiotic prophylaxis in clean-contaminated head and neck oncologic surgery, suppl 155:16
  Antimicrobial prophylaxis for recurrent acute otitis media, suppl 155:33
  Antimicrobial use in otolaryngeal infections: general considerations, suppl 155:5
  Effect of prior antibiotic treatment of middle ear disease in children, 87

Antigen
  Bovine temporal bone as source of inner ear antigen, 688

Approach
  Transmandibular transpterygoid approach to nasopharynx, parapharyngeal space, and skull base, 383

Arginine vasopressin
  Syndrome of inappropriate secretion of arginine vasopressin in patients with cancer of head and neck, 946

Arytenoid adduction
  Physiologic assessment of arytenoid adduction, 321

Aspiration
  Consumer product aspiration and ingestion in children: analysis of emergency room reports to National Electronic Injury Surveillance System, 739

Atelectasis
  Fascia and perichondrium atrophy in tympanoplasty and recurrent middle ear atelectasis, 755
  Maxillary sinus atelectasis, 977
  Rounded atelectasis, 538

Atherosclerosis
  Irradiation-induced atheroslerosis: factor in therapeutic planning, 222

Auditory processing
  Reading skills and auditory processing ability in children with chronic otitis media in early childhood, 530

Autoimmunity
  Cochlear and renal pathology in autoimmune strain mouse, suppl 157:87
  Corneal autoimmunity in Cogan's syndrome? Report of two cases, 679
  Spontaneous remission in experimental autoimmune labyrinthitis, 1007

Bacteriology
  Aerobic bacteriology of chronic suppurative otitis media without cholesteatoma in children, 866

Biopsy
  Pediatric transbronchial lung biopsy, 135

Blood
  Cochlear blood flow and microvascular resistance changes in response to hypertonic glycerol, urea, and mannitol infusions, 168
  Effect of blood transfusion on recurrence of head and neck carcinoma. Retrospective review and meta-analysis, 724

Book Reviews
  Ballenger JJ, ed. *Diseases of the Nose, Throat, Ear, Head and Neck*, 628
  Blaustein DI, Heffez LB. *Arthroscopic Atlas of the Temporomandibular Joint*, 189
  Cady B, Rossi RL. *Surgery of the Thyroid and Parathyroid Glands*, 628
  Davis RK. *Lasers in Otolaryngology–Head and Neck Surgery*, 189
  Dedo HH. *Surgery of the Larynx and Trachea*, 189
  Fireman P, Slavin RG, eds. *Atlas of Allergies*, 627
  Guilleminault C, Paratinen M, eds. *Obstructive Sleep Apnea Syndrome: Clinical Research and Treatment*, 189
  Hanafee WN, Ward PH, eds. *The Larynx: Radiology-Surgery-Pathology*, 190
  McCurdy JA Jr. *Cosmetic Surgery of the Asian Face*, 190
  Naspitz CK, Tinkelman DG, eds. *Childhood Rhinitis and Sinusitis: Pathophysiology and Treatment*, 190
  Paparella MM, Shumrick DA, Gluckman JL, Meyerhoff WL, eds. *Otolaryngology*, 626
  Settipane GA, ed. *Rhinitis*, 628

Botulinum toxin
  Point-touch technique of botulinum toxin injection for treatment of spasmodic dysphonia, 883
  Quantitative mapping of effect of botulinum toxin injections in thyroarytenoid muscle, 888

Brain stem auditory evoked potential
  Computer recognition of brain stem auditory evoked potential wave V by neural network, 782

Branchial fistula
  Pull-through branchial fistulectomy: technique for otolaryngologist, 501

Calcification
  Calcification of internal auditory canal tumors, 620

Calcium phosphate
  Macroporous biphasic calcium phosphate efficiency in mastoid cavity obliteration: experimental and clinical findings, 669

Cancer
  Carotid artery resection for head and neck cancer, 778
  Dysphagia following various degrees of surgical resection for oral cancer, 138
  Heterogeneity in epidermal growth factor responsiveness and tumor growth of human maxillary cancer cell lines, 519
  Meta-analysis of second malignant tumors in head and neck cancer: case for endoscopic screening protocol, 105
  Syndrome of inappropriate secretion of arginine vasopressin in patients with cancer of head and neck, 946

Carcinoma
  Laser surgery for treatment of larynx carcinomas: indications, techniques, and preliminary results, 113
  Nonsquamous carcinomas of larynx, 1024
  Tracheobronchial obstruction from esophageal carcinoma: bronchoscopic treatment with neodymium:yttrium-aluminum-garnet laser, 556
  Voice analysis of patients with endoscopically treated early laryngeal carcinoma, 142

Carotid artery
  Carotid artery resection for head and neck cancer, 778

Cartilaginous tumor
  Cartilaginous tumor of larynx, 617

Cervical abscess
  Radiographic analysis of deep cervical abscesses, 854

Charge barrier
  Alterations of charge barrier in inner ear following immune reactions, suppl 157:63

Choanal atresia
  Bilateral choanal atresia associated with malformation of anterior skull base: embryogenesis and clinical implications, 916

Cholesteatoma
  Immunohistochemical analysis of cytokeratin expression in middle ear cholesteatoma and related epithelial tissues, 931
  Interleukin-1 of cholesteatomatous keratinocytes, suppl 157:32

Chondroblastoma
  Chondroblastoma of temporal bone. Case report and literature review, 763

Chondrosarcoma
  Chondrosarcoma of larynx, 183

Cilia
  Ultrastructural changes in human nasal cilia caused by common cold and recovery of ciliated epithelium, 982

Cisplatin
  Combined effects of noise and cisplatin: short- and long-term follow-up, 969

Cleft palate
  Elastin at hinge portion of eustachian tube cartilage in specimens from normal subjects and those with cleft palate, 163
  Minuscule submucous cleft palate. Cadaver study, 417

Cochlea
  Cochlear and renal pathology in autoimmune strain mouse, suppl 157:87
  Cochlear blood flow and microvascular resistance changes in response to hypertonic glycerol, urea, and mannitol infusions, 168
  Membranous cytoplasmic bodies in lateral wall of cat cochlea, 355

Cochlear implant
  Comparison of speech recognition ability with different speech processing strategies by Korean cochlear implantees, 659
  Diameter of cochlear nerve in deaf humans: implications for cochlear implantation, 988
  Factors contributing to phoneme recognition ability of users of 22-channel cochlear implant system, 32
  Factors predicting postoperative sentence scores in postlinguistically deaf adult cochlear implant patients, 342
  Management of flap necrosis in cochlear implantation, 38
  Model for understanding influence of some parameters in cochlear implantation, 42

Cogan's syndrome
  Corneal autoimmunity in Cogan's syndrome? Report of two cases, 679

Cold
  Ultrastructural changes in human nasal cilia caused by common cold and recovery of ciliated epithelium, 982

Collagen
  Collagen in developing larynx. Preliminary study, 328
  Localization of type IV collagen and laminin in guinea pig inner ear, suppl 157:58
  Role of injectable collagen in treatment of glottic insufficiency: study of 119 patients, 237

Communication
  Communication status following laryngectomy: Iowa experience 1984-1987, 503

Compensation
  Vestibulo-ocular compensation following unilateral vestibular deafferentation, 525

Complications
  Airway and other complications of percutaneous endoscopic gastrostomy in head and neck cancer patients, 310
  Complications of percutaneous endoscopic gastrostomy in head and neck cancer patients, 46
  Hearing loss as sequel of lumbar puncture, 390
  Lower complication rates associated with bronchial foreign bodies over last 20 years, 61

Computer Applications in Otolarynology
  Computer recognition of brain stem auditory evoked potential wave V by neural network, 782

Congenital disorders
  Bilateral choanal atresia associated with malformation of anterior skull base: embryogenesis and clinical implications, 916
  Congenital lack of olfactory ability, 229
  Meniere's syndrome inherited as autosomal dominant trait, 590
  Otolaryngologic manifestations of mucopolysaccharidoses, 472
  Temporal bone findings in keratitis, ichthyosis, and deafness syndrome. Case report, 413
  Tracheal agenesis, 560

Continuous positive airway pressure
  Continuous positive airway pressure as promoter of laryngospasm during halothane anesthesia, 893

Corticosteroids
  Recovery from repeated sudden hearing loss with corticosteroid use in presence of acoustic neuroma, 827

Cranial nerve
  Electrophysiologic investigation of lower cranial nerve diseases by means of magnetically stimulated neuromyography of larynx, 629

Cricopharyngeal myotomy
  Cricopharyngeal myotomy: indications and technique, 216

Cricothyroid muscle
  Three bellies of canine cricothyroid muscle, suppl 156

Cytokeratin
  Immunohistochemical analysis of cytokeratin expression in middle ear cholesteatoma and related epithelial tissues, 931

Cytokines
  Immunologic characteristics of cytokines in otitis media with effusion, suppl 157:21

Decannulation
  Pediatric airway reconstruction at Great Ormond Street: ten-year review. III. Decannulation and suprastomal collapse, 656

Dehiscence
  Facial canal dehiscence: histologic study and computer reconstruction, 925

Development
  Collagen in developing larynx. Preliminary study, 328

Dexamethasone
  Effects of aerosolized dexamethasone on acute subglottic injury, 95

Dissection
  Functional neck dissection: three decades of controversy, 339

DNA hybridization
  Detection of human papillomavirus infection in diseased and nondiseased sites of respiratory tract in recurrent respiratory papillomatosis patients by DNA hybridization, 408

Double aortic arch, 872

Dumbbell tumor
  Skull base dumbbell tumor: surgical experience with two adolescents, 939

Dysphagia
  Dysphagia following various degrees of surgical resection for oral cancer, 138

Ear
  Immunologic studies on ear, suppl 157
  The ear: audio-visual tour through America's favorite sensory organ. Version 1.1, 870

Editorial
  Are We Ready for the Year 2001?, 543
  The Future: What Does It Hold?, 1

Electrocochleography
  Electrocochleography in presence and absence of perilymphatic fistula, 403
  Interpretation of electrocochleography in Meniere's disease and normal subjects, 496

Electromyography
  Intraoperative laryngeal electromyographic assessment of patients with immobile vocal fold, 799
  Multichannel electromyographic observations in spasmodic dysphonia patients and normal control subjects, 67

Endolymphatic sac
  Distribution of immunocompetent cells in endolymphatic sac, suppl 157:39
  Endolymphatic hydrops induced by immune response of endolymphatic sac: relation to perilymph antibody levels, suppl 157:48
  Vestibular disorders following immune response of endolymphatic sac in guinea pig, suppl 157:54

Endotoxin
  Effect of endotoxin on cultured chinchilla middle ear epithelium, 607

Epidermal growth factor
  Heterogeneity in epidermal growth factor responsiveness and tumor growth of human maxillary cancer cell lines, 519

Epidermolysis bullosa
  Junctional epidermolysis bullosa of larynx. Report of case and literature review, 861

Epiglottis prolapse
  Acquired laryngomalacia: epiglottis prolapse as cause of airway obstruction, 314

Epithelial-myoepithelial carcinoma
  Epithelial-myoepithelial carcinoma of salivary glands, 540

Erythromycin
  Erythromycin inhibition of lipopolysaccharide-stimulated tumor necrosis factor alpha production by human monocytes in vitro, suppl 157:16

Esophagoscopy
  Open tube versus flexible esophagoscopy in adult head and neck endoscopy, 147

Eustachian tube
  Clearance function of eustachian tube and negative middle ear pressure, 759
  Distributions of eustachian tube goblet cells and glands in children with and without otitis media, 750
  Elastin at hinge portion of eustachian tube cartilage in specimens from normal subjects and those with cleft palate, 163
  Pathogenesis of experimental otitis media with effusion caused by combination of eustachian tube dysfunction and immunosuppression, suppl 157:4

Exotoxin
  Inner ear damage and passage through round window membrane of *Pseudomonas aeruginosa* exotoxin A in chinchilla model, 437

Facial canal
  Facial canal dehiscence: histologic study and computer reconstruction, 925

Fibrous dysplasia
  Fibrous dysplasia of sphenoid sinus, 100
  Three-dimensional computed tomography in case of craniofacial fibrous dysplasia, 275

Fine-needle aspiration
  Fine-needle aspiration of salivary glands: its utility and tissue effects, 185

Fistula
  Chronic perilymph fistula in guinea pig with implications in human, 176
  Electrocochleography in presence and absence of perilymphatic fistula, 403
  Pull-through branchial fistulectomy: technique for otolaryngologist, 501
  Vestibular pathophysiologic changes in experimental perilymphatic fistula, 612

Flap
  Laryngotracheal reconstruction in adults with sternocleidomastoid myoperiosteal flap, 897
  Perichondrial microvascular free transfer: creation of compound flap for laryngeal reconstruction in rabbits, 265

Foreign body
  Lower complication rates associated with bronchial foreign bodies over last 20 years, 61

Fracture
  Stable internal fixation of fractures of partially mineralized thyroid cartilage, 76

Gas
  Theoretic analysis of middle ear gas composition under conditions of nonphysiologic ventilation, 445

Gastroesophageal reflux
  Pediatric airway manifestations of gastroesophageal reflux, 742

Gastrostomy
  Airway and other complications of percutaneous endoscopic gastrostomy in head and neck cancer patients, 310
  Complications of percutaneous endoscopic gastrostomy in head and neck cancer patients, 46

Giant air cell
  Giant air cell of petrous apex: possible cause of facial hypalgesia, 685

Glomus tumor
  Does intervention improve natural course of glomus tumors? Series of 108 patients seen in 32-year period, 635

Glottic insufficiency
  Role of injectable collagen in treatment of glottic insufficiency: study of 119 patients, 237

Graft
  Experimental tracheal replacement using revascularized jejunal autograft with implantable Dacron mesh tube, 807
  Histopathologic correlates of acute laryngeal allograft rejection in rat model, 156
  Rat model for vascularized laryngeal allograft, 950

Granuloma
  Plasma cell granuloma of middle ear and mastoid. Case report, 92

Hematoma
  Intraparotid hematoma, 791

Herpes zoster oticus
  Herpes zoster oticus: treatment with acyclovir, 161

Human papillomavirus
  Detection of human papillomavirus infection in diseased and nondiseased sites of respiratory tract in recurrent respiratory papillomatosis patients by DNA hybridization, 408

Hydrops
  Endolymphatic hydrops induced by immune response of endolymphatic sac: relation to perilymph antibody levels, suppl 157:48

Hypalgesia
  Giant air cell of petrous apex: possible cause of facial hypalgesia, 685

Imaging
  Experimental otitis media evaluated by magnetic resonance imaging: in vivo model, 248
  Labyrinthine enhancement on gadolinium-enhanced magnetic resonance imaging in sudden deafness and vertigo: correlation with audiologic and electronystagmographic studies, 459

Imaging Case Study of the Month
  Aneurysm of anterior inferior cerebellar artery producing hearing loss, 705
  Bone scan diagnosis of masked mastoiditis, 707
  Calcification of internal auditory canal tumors, 620
  Cartilaginous tumor of larynx, 617
  Chondrosarcoma of larynx, 183
  Cystic squamous cell carcinoma metastatic to neck from occult primary, 1021
  Double aortic arch, 872
  Fibrous dysplasia of sphenoid sinus, 100
  Intraparotid hematoma, 791
  Magnetic resonance angiography of synchronous bilateral carotid body paragangliomas and bilateral vagal paragangliomas, 955
  Massive osteolysis (Gorham's disease) of temporomandibular joint, 1018
  Metastatic tumor presenting as chronic otitis and facial paralysis, 280
  Noninvasive radiologic options in evaluating intracranial complications of otitis media, 363
  Penetrating trauma of jugular foramen, 452
  Rounded atelectasis, 538
  Three-dimensional computed tomography in case of craniofacial fibrous dysplasia, 275
  Utility of magnetic resonance imaging in detection of subdural empyema, 876
  Vagal schwannoma, 360

Immobilization
  New device for interdental immobilization, 776

Immunity
  Alterations of charge barrier in inner ear following immune reactions, suppl 157:63
  Antibodies against 30 kilodalton cochlear protein and type II and IX collagens in serum of patients with inner ear diseases, 1000
  Distribution of immunocompetent cells in endolymphatic sac, suppl 157:39
  Immunologic studies on ear, suppl 157
  Inhibition of nasopharyngeal colonization of *Hemophilus influenzae* by oral immunization, suppl 157:11
  Mechanism of immune complex–mediated inner ear diseases, suppl 157:72

In situ hybridization
  In situ hybridization and laryngeal papillomas, 119

Indium 111
  Indium 111–labeled leukocyte scintigraphy in evaluating head and neck infections, 961

Infectious disease
  Current issues in ENT infectious disease, suppl 155

Ingestion
  Consumer product aspiration and ingestion in children: analysis of emergency room reports to National Electronic Injury Surveillance System, 739

Injury
  Effects of aerosolized dexamethasone on acute subglottic injury, 95
  Experimental blunt injury to larynx, 270

Inner ear
  Bovine temporal bones as source of inner ear antigen, 688
  Mechanism of immune complex–mediated inner ear diseases, suppl 157:72
  Type I allergy in inner ear of guinea pig, suppl 157:78

Inspiratory speech
  Inspiratory speech as management option for spastic dysphonia. Case study, 375

Interdental immobilization
  New device for interdental immobilization, 776

Interleukins
  Detection of regulatory factors of lymphokine-activated killer cell activity in head and neck cancer patients treated with interleukin-2, 909
  Interleukin-1 of cholesteatomatous keratinocytes, suppl 157:32

Intermediate filament protein
  Expression of intermediate filament proteins in adult human vestibular labyrinth, 479

Interneurons
  Quantitative ultrastructural study of cat abducens interneurons, 691

Intubation
  Subglottic ulceration and healing following endotracheal intubation in neonate: morphometric study, 815

Irradiation
  Effect of radioprotector WR2721 on irradiation-induced injury to ciliated cells of eustachian tube, 395
  Irradiation-induced atherosclerosis: factor in therapeutic planning, 222

Jejunal graft
  Free jejunal graft: effects of longitudinal myotomy, 333

Junctional epidermolysis bullosa
  Junctional epidermolysis bullosa of larynx. Report of case and literature review, 861

Keratitis, ichthyosis, and deafness syndrome
  Temporal bone findings in keratitis, ichthyosis, and deafness syndrome. Case report, 413

Labyrinth
  Labyrinthine enhancement on gadolinium-enhanced magnetic resonance imaging in sudden deafness and vertigo: correlation with audiologic and electronystagmographic studies, 459
  Spontaneous remission in experimental autoimmune labyrinthitis, 1007

Laminin
  Localization of type IV collagen and laminin in guinea pig inner ear, suppl 157:58

Laryngeal adenocarcinoma
  Laryngeal adenocarcinoma, not otherwise specified, treated with carbon dioxide laser excision and postoperative radiotherapy, 920

Laryngeal amyloid
  Organ-limited laryngeal amyloid deposits: clinical, morphological, and immunohistochemical results of five cases, 770

Laryngeal cartilage
  Experimental blunt injury to larynx, 270

Laryngeal efficiency
  Noninvasive technique for estimating subglottic pressure and laryngeal efficiency, 578

Laryngectomy
  Communication status following laryngectomy: Iowa experience 1984-1987, 503

Laryngomalacia
  Acquired laryngomalacia: epiglottis prolapse as cause of airway obstruction, 314

Laryngoscopy
  Comparison of new telescopic video microlaryngoscopic and standard microlaryngoscopic techniques, 51

Laryngospasm
  Continuous positive airway pressure as promoter of laryngospasm during halothane anesthesia, 893

Laryngotracheal stenosis
  Stenting for pediatric laryngotracheal stenosis, 651

Laryngotracheoplasty
  Pediatric airway reconstruction at Great Ormond Street: ten-year review. I. Laryngotracheoplasty and laryngotracheal reconstruction, 465

Laser
  Laser surgery for treatment of larynx carcinomas: indications, techniques, and preliminary results, 113
  Tracheobronchial obstruction from esophageal carcinoma: bronchoscopic treatment with neodymium:yttrium-aluminum-garnet laser, 556
  Treatment of tracheal and endobronchial lesions with potassium titanyl phosphate laser, 205

Leprosy
  Lepromatous leprosy: nasal manifestations and treatment with minocycline, 261

Letters to the Editor, 371, 372, 798

Lidocaine
  Lidocaine effects on laryngeal chemoreflex, mechanoreflex, and afferent electrical stimulation reflex, 583

Lithiasis
  Angiolithiasis and sialolithiasis in head and neck, 455

Lumbar puncture
  Hearing loss as sequel of lumbar puncture, 390

Lung
  Pediatric transbronchial lung biopsy, 135

Lymphokine
  Detection of regulatory factors of lymphokine-activated killer cell activity in head and neck cancer patients treated with interleukin-2, 909

Mastoid cavity obliteration
  Macroporous biphasic calcium phosphate efficiency in mastoid cavity obliteration: experimental and clinical findings, 669

Mastoiditis
  Bone scan diagnosis of masked mastoiditis, 707

Membranous cytoplasmic bodies
  Membranous cytoplasmic bodies in lateral wall of cat cochlea, 355

Meniere's disease
  Interpretation of electrocochleography in Meniere's disease and normal subjects, 496
  Ménière's symptom complex: medical treatment, 20
  Meniere's syndrome inherited as autosomal dominant trait, 590

Metastasis
  Cystic squamous cell carcinoma metastatic to neck from occult primary, 1021
  Metastatic tumor presenting as chronic otitis and facial paralysis, 280

Middle ear
  Clearance function of eustachian tube and negative middle ear pressure, 759
  Effect of endotoxin on cultured chinchilla middle ear epithelium, 607
  Presence of 80 kilodalton protein, cross-reacted with monoclonal antibodies to pulmonary surfactant protein A, in human middle ear, 491
  Theoretic analysis of middle ear gas composition under conditions of nonphysiologic ventilation, 445
  Transmission properties of middle ear, 191

Minocycline
  Lepromatous leprosy: nasal manifestations and treatment with minocycline, 261

Model
  Animal model for ischemic facial nerve paralysis with selective vascular embolization, 423
  Model for understanding influence of some parameters in cochlear implantation, 42
  MRL/MP-*lpr/lpr* mouse as model of immune-induced sensorineural hearing loss, suppl 157:82
  Rat model for vascularized laryngeal allograft, 950

Mucopolysaccharidosis
  Otolaryngologic manifestations of mucopolysaccharidoses, 472

Muscle
  Single motor unit activity of human intrinsic laryngeal muscles during respiration, 832
  Three bellies of canine cricothyroid muscle, suppl 156

Mutation
  Malformation and degeneration in inner ear of *mos* transgenic mice, 430

Myotomy
  Cricopharyngeal myotomy: indications and technique, 216
  Free jejunal graft: effects of longitudinal myotomy, 333

Nasopharynx
  Inhibition of nasopharyngeal colonization of *Hemophilus influenzae* by oral immunization, suppl 157:11

Neck
  Functional neck dissection: three decades of controversy, 339

Necrosis
  Management of flap necrosis in cochlear implantation, 38
  Necrotizing sialometaplasia, 282

Nerve
  Causes of facial nerve paresis after translabyrinthine surgery for acoustic neuroma, 821
  Characteristics of late responses to superior laryngeal nerve stimulation in humans, 127
  Diameter of cochlear nerve in deaf humans: implications for cochlear implantation, 988

Neuroendocrine tumor
  Neuroendocrine tumors of larynx, 710

Neuromyography
  Electrophysiologic investigation of lower cranial nerve diseases by means of magnetically stimulated neuromyography of larynx, 629

Neutrophil elastase
  Neutrophil elastase and its complex with alpha 1-antitrypsin in pathogenesis of chronic suppurative otitis media, suppl 157:26

Noise
  Combined effects of noise and cisplatin: short- and long-term follow-up, 969

Obituaries
  Bruce Proctor, 797
  Heinrich Hans Spoendlin, 458

Olfaction
  Congenital lack of olfactory ability, 229

Open tube esophagoscopy
  Open tube versus flexible esophagoscopy in adult head and neck endoscopy, 147

Optokinetic afternystagmus
  Slow cumulative eye position to quantify optokinetic afternystagmus, 255

Orbit
  Orbital complications of acute sinusitis: comparison of computed tomography scan and surgical findings, 598

Osteolysis
  Massive osteolysis (Gorham's disease) of temporomandibular joint, 1018

Otitis media
  Aerobic bacteriology of chronic suppurative otitis media without cholesteatoma in children, 866
  Detection of genomic sequences of respiratory syncytial virus in otitis media with effusion in children, suppl 157:7

Distributions of eustachian tube goblet cells and glands in children with and without otitis media, 750
Effect of prior antibiotic treatment on middle ear disease in children, 87
Experimental otitis media evaluated by magnetic resonance imaging: in vivo model, 248
Histopathology of tubotympanum of children with otitis media treated with ventilation tubes, 841
Immunologic characteristics of cytokines in otitis media with effusion, suppl 157:21
Inner ear damage and passage through round window membrane of *Pseudomonas aeruginosa* exotoxin A in chinchilla model, 437
Neutrophil elastase and its complex with alpha 1-antitrypsin in pathogenesis of chronic suppurative otitis media, suppl 157:26
Noninvasive radiologic options in evaluating intracranial complications of otitis media, 363
Otitis media update: pathogenesis and treatment, suppl 155:21
Pathogenesis of experimental otitis media with effusion caused by combination of eustachian tube dysfunction and immunosuppression, suppl 157:4
Reading skills and auditory processing ability in children with chronic otitis media in early childhood, 530

Otoacoustic emissions
Influence of general anesthesia on transiently evoked otoacoustic emissions in humans, 994

Otolaryngology
Forty questions in otolaryngology. (Suggestion box for young investigators), 715

Otolith-ocular reflex
Off-vertical axis rotation: test of otolith-ocular reflex, 643

Otosclerosis
The surgery of otosclerosis, 546

Papilloma
In situ hybridization and laryngeal papillomas, 119

Paraganglioma
Magnetic resonance angiography of synchronous bilateral carotid body paragangliomas and bilateral vagal paragangliomas, 955
Thyroid paraganglioma, 293

Paralysis
Animal model for ischemic facial nerve paralysis with selective vascular embolization, 423
Injection and removal of Teflon for unilateral vocal cord paralysis, 81
Intraoperative laryngeal electromyographic assessment of patients with immobile vocal fold, 799
Physiologic assessment of arytenoid adduction, 321
Videostroboscopy of human vocal fold paralysis, 567

Pathology Consultation
"Adenocarcinoma, not otherwise specified": diminishing group of salivary carcinomas, 102
Amyloidosis in upper aerodigestive tracts, 794
Angiolithiasis and sialolithiasis in head and neck, 455
Choanal and angiomatous polyps of sinonasal tract, 623
Embryoma (sialoblastoma) of salivary glands, 958
Epithelial-myoepithelial carcinoma of salivary glands, 540
Fine-needle aspiration of salivary glands: its utility and tissue effects, 185
Necrotizing sialometaplasia, 282
Neuroendocrine tumors of larynx, 710
Nonsquamous carcinomas of larynx, 1024
Rhinoscleroma and rhinosporidiosis, 879
Synovial sarcomas of head and neck, 367

Perforation
Conservative medical management of traumatic pharyngoesophageal perforations, 209

Perilymph
Chronic perilymph fistula in guinea pig with implications in human, 176
Vestibular pathophysiologic changes in experimental perilymphatic fistula, 612

Pharyngitis
Etiology and management of pharyngitis and pharyngotonsillitis in children: current review, suppl 155:51

Phonation
Phonation and swallowing considerations in pediatric laryngotracheal reconstruction, 731

Phoneme recognition
Factors contributing to phoneme recognition ability of users of 22-channel cochlear implant system, 32

Planum semilunatum
Planum semilunatum of rat: new light and electron microscopy observations, 601

Plasma cell
Plasma cell granuloma of middle ear and mastoid. Case report, 92

Plasmacytoma
Solitary plasmacytoma of skull base, 665

Polyps
Choanal and angiomatous polyps of sinonasal tract, 623

Potassium titanyl phosphate laser
Treatment of tracheal and endobronchial lesions with potassium titanyl phosphate laser, 205

Prediction
Factors predicting postoperative sentence scores in postlinguistically deaf adult cochlear implant patients, 342

Protein
Antibodies against 30 kilodalton cochlear protein and type II and IX collagens in serum of patients with inner ear diseases, 1000
Presence of 80 kilodalton protein, cross-reacted with monoclonal antibodies to pulmonary surfactant protein A, in human middle ear, 491

Radioprotector WR2721
Effect of radioprotector WR2721 on irradiation-induced injury to ciliated cells of eustachian tube, 395

Reconstruction
Laryngotracheal reconstruction in adults with sternocleidomastoid myoperiosteal flap, 897
Pediatric airway reconstruction at Great Ormond Street: ten-

year review. III. Decannulation and suprastomal collapse, 656
  Pediatric airway reconstruction at Great Ormond Street: ten-year review. I. Laryngotracheoplasty and laryngotracheal reconstruction, 465
  Pediatric airway reconstruction at Great Ormond Street: ten-year review. II. Revisional airway reconstruction, 595
  Perichondrial microvascular free transfer: creation of compound flap for laryngeal reconstruction in rabbits, 265
  Phonation and swallowing considerations in pediatric laryngotracheal reconstruction, 731

Recurrence
  Effect of blood transfusion on recurrence of head and neck carcinoma. Retrospective review and meta-analysis, 724

Reflex
  Lidocaine effects on laryngeal chemoreflex, mechanoreflex, and afferent electrical stimulation reflex, 583

Reflux
  Pediatric airway manifestations of gastroesophageal reflux, 742

Regression
  Spontaneous regression of juvenile nasopharyngeal angiofibroma, 469

Respiration
  Single motor unit activity of human intrinsic laryngeal muscles during respiration, 832

Respiratory syncytial virus
  Detection of genomic sequences of respiratory syncytial virus in otitis media with effusion in children, suppl 157:7
  Immunologic response of adenoidal lymphocytes to respiratory syncytial virus, 848

Revision
  Pediatric airway reconstruction at Great Ormond Street: ten-year review. II. Revisional airway reconstruction, 595

Rhinoscleroma
  Rhinoscleroma and rhinosporidiosis, 879

Rotation
  Off-vertical axis rotation: test of otolith-ocular reflex, 643

Sarcoma
  Synovial sarcomas of head and neck, 367

Schwannoma
  Vagal schwannoma, 360

Scintigraphy
  Indium 111–labeled leukocyte scintigraphy in evaluating head and neck infections, 961

Screening
  Meta-analysis of second malignant tumors in head and neck cancer: case for endoscopic screening protocol, 105

Sensorineural hearing loss
  MRL/MP-*lpr*/*lpr* mouse as model of immune-induced sensorineural hearing loss, suppl 157:82

Sialoblastoma
  Embryoma (sialoblastoma) of salivary glands, 958

Sicca syndrome
  Primary salivary gland amyloidosis causing sicca syndrome, 487

Sinuses
  Maxillary sinus atelectasis, 977
  Medical and surgical management of sinusitis in adults, suppl 155:46
  Orbital complications of acute sinusitis: comparison of computed tomography scan and surgical findings, 598
  Sinusitis in infants and children, suppl 155:37
  Surgical management of sinus disease in children, suppl 155:42

Skull base
  Skull base dumbbell tumor: surgical experience with two adolescents, 939
  Solitary plasmacytoma of skull base, 665

Slow cumulative eye position
  Slow cumulative eye position to quantify optokinetic afternystagmus, 255

Software Review
  Cochlear anatomy: Macintosh tour, 1015
  The ear: audio-visual tour through America's favorite sensory organ. Version 1.1, 870
  The TMJ scale: including computer program disk and 74-page illustrated manual, 954

Spasmodic dysphonia
  Inspiratory speech as management option for spastic dysphonia. Case study, 375
  Multichannel electromyographic observations in spasmodic dysphonia patients and normal control subjects, 67
  Point-touch technique of botulinum toxin injection for treatment of spasmodic dysphonia, 883
  Quantitative mapping of effect of botulinum toxin injections in thyroarytenoid muscle, 888

Speech recognition
  Comparison of speech recognition ability with different speech processing strategies by Korean cochlear implantees, 659

Sphenopalatine ganglion
  Surgical removal of sphenopalatine ganglion. Report of three operations: elaborating original technic to expose pterygopalatine fossa, command internal maxillary artery and its terminals and infraorbital nerve and its branches, 285

Spiral modiolar vein
  Spiral modiolar vein: its importance in viral load of inner ear, suppl 157:67

Stenosis
  Stenting for pediatric laryngotracheal stenosis, 651

Subdural empyema
  Utility of magnetic resonance imaging in detection of subdural empyema, 876

Subglottic pressure
  Noninvasive technique for estimating subglottic pressure and laryngeal efficiency, 578

Submucous cleft palate
  Minuscule submucous cleft palate. Cadaver study, 417

Superior laryngeal nerve
  Characteristics of late responses to superior laryngeal nerve stimulation in humans, 127

Teflon
  Injection and removal of Teflon for unilateral vocal cord paralysis, 81

Temporal bone
  Anatomy of guinea pig temporal bone, 699
  Chondroblastoma of temporal bone. Case report and literature review, 763

Temporomandibular joint
  The TMJ scale: including computer program disk and 74-page illustrated manual, 954

Thyroid cartilage
  Stable internal fixation of fractures of partially mineralized thyroid cartilage, 76

Thyroid paraganglioma, 293

Tonsillectomy
  Current indications for tonsillectomy and adenoidectomy, suppl 155:58

Trachea
  Experimental tracheal replacement using revascularized jejunal autograft with implantable Dacron mesh tube, 807
  Tracheal agenesis, 560

Tracheobronchomalacia
  Pediatric tracheobronchomalacia and major airway collapse, 300

Transgenic mice
  Malformation and degeneration in inner ear of *mos* transgenic mice, 430

Transmandibular transpterygoid approach
  Transmandibular transpterygoid approach to nasopharynx, parapharyngeal space, and skull base, 383

Trauma
  Conservative medical management of traumatic pharyngoesophageal perforations, 209
  Penetrating trauma of jugular foramen, 452

Tremor
  Rapid voice tremor, or "flutter," in amyotrophic lateral sclerosis, 511

Tubotympanum
  Histopathology of tubotympanum of children with otitis media treated with ventilation tubes, 841

Tumor
  Does intervention improve natural course of glomus tumors? Series of 108 patients seen in 32-year period, 635

Tumor necrosis factor alpha
  Erythromycin inhibition of lipopolysaccharide-stimulated tumor necrosis factor alpha production by human monocytes in vitro, suppl 157:16

Tympanoplasty
  Fascia and perichondrium atrophy in tympanoplasty and recurrent middle ear atelectasis, 755

Ulcer
  Subglottic ulceration and healing following endotracheal intubation in neonate: morphometric study, 815

Vestibular labyrinth
  Expression of intermediate filament proteins in adult human vestibular labyrinth, 479

Vestibule
  Vestibular disorders following immune response of endolymphatic sac in guinea pig, suppl 157:54
  Vestibulo-ocular compensation following unilateral vestibular deafferentation, 525

Video
  Comparison of new telescopic video microlaryngoscopic and standard microlaryngoscopic techniques, 51
  Videostroboscopy of human vocal fold paralysis, 567

Viral load
  Spiral modiolar vein: its importance in viral load of inner ear, suppl 157:67

Voice
  Voice analysis of patients with endoscopically treated early laryngeal carcinoma, 142

Wound healing
  Angiogenic growth factors: their effects and potential in soft tissue wound healing, 349

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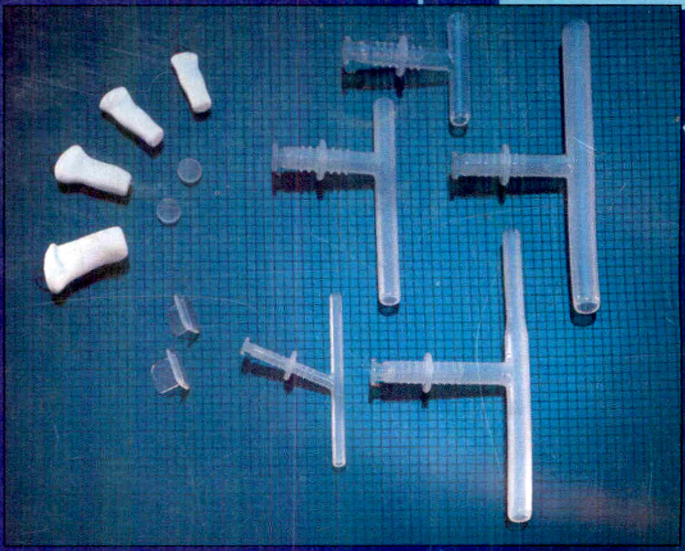

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